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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
December 21, 2005
Radisson Hotel SeaTac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D.
Robert Bray, M.D.
Carol Cordy, M.D, (Vice Chair)
Alvin Goo, Pharm D.
Jason Iltz, Pharm D. (via teleconference)
Janet Kelly, Pharm D.
T. Vyn Reese, M.D.
Patti Varley, ARNP
Daniel Lessler, MD

9:00 a.m. - Committee came to order.

WELCOME & INTRODUCTIONS

Jeff Graham, MD: We have people on the telephone today and for them to hear us…this is Jeff Graham speaking…we need to talk into the microphone when you're speaking. I want to draw your attention to our schedule for next year. It's posted on our web site. That's www.rx.wa.gov. And that…you will see that we will have six meetings next year. The meetings are what I say in the event months like February, April and as always the third Wednesday of that month. So we have a very complete agenda posted on our web site for next year. I think those are the only announcements we have at this time. So maybe, Dan, we could have the committee introduce themselves at the table.

Dan Lessler, MD: Okay. Why don't we go around and introduce ourselves. I'm Dan Lessler and I am Chair of the committee.

Patti Varley, ARNP: Patti Varley, Child and Adolescent Psych Clinical Nurse specialist from Children's, part of the P&T.

Carol Cordy, MD: Carol Cordy, family medicine culture of the committee.

Robert Bray, MD: Bob Bray from Spokane. Family physician and part of the P&T committee.

Alvin Goo, Pharm D: Alvin Goo, P&T committee, pharmacy and family medicine.

T. Vyn Reese, MD: Vyn Reese, geriatric in internal medicine. I'm on the committee.

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* For copies of the official audio taped record of this meeting, please contact Regina Chacon at (206)521-2027 pdp@hca.wa.gov.

Jeff Graham, MD: And then I think Jason. Oh, Angelo. I'm sorry.

Angelo Ballasiotes, Pharm D: Angelo Ballasiotes, Central Washington Conference in Mental Health in Yakima.

Jeff Graham, MD: Oh, and Janet is here, sorry.

Janet Kelly: Janet Kelly, pharmacist and member of the P&T.

Jason Iltz, MD: Good morning. It's Jason Iltz on the phone, pharmacist member of the P&T.

Jeff Graham, MD: Okay. Thank you. I would also like to introduce Barney Speight who is our assistant deputy…or Deputy Administrator for the Healthcare Authority. So we are very pleased to have you here today. Welcome.

Dan Lessler, MD: Well, our first order of business actually is to clarify a recommendation on Ticlodipine, which is one of the anti-platelet agents that I believe was considered last time and actually, Jeff, I was going to ask since I was talking to some of my colleagues here. If you could just clarify exactly what you need from us.

Jeff Graham, MD: Well, when we reviewed that class where we're…recommendations for the two other drugs within that class—Plavix and Aggrenox and we didn't say anything about TICLID at all whether it should be on the Preferred Drug List. It doesn't mean it has to be preferred. Or…I know there were some safety issues brought up at that time. So…and previously when we've had some issues around there and we've left a drug off in a class it is sort of deliberate, but this time it was sort of like it we just didn't…and staff didn't pick that up until we went to look at the recommendations as to what we should do from then on with that drug.

Dan Lessler, MD: So my understanding of the discussion last time around was that there was some discussion around Ticlodipine specifically around some of the safety issues and perhaps it's having some risks that weren't associated with the agents and so I think that's probably the basis for…

T. Vyn Reese, MD: This is Dr. Reese and my memory serves me we did talk about TICLID about the safety issues and maybe it just didn't get into the tapes, but we said it was a safety concern and we didn't want it on the formulary. That was my recollection of it, but maybe…I don't know if other people remember it the same way I did. But that was the discussion the last time. I'm pretty certain we did mention that we were quite concerned about safety issues of that drug.

Dan Lessler, MD: Are there other comments in terms of the discussion around TICLID?

Jeff Graham, MD: This is Jeff Graham. That was correct. It's just that we didn't really make a very specific recommendation about it.

Dan Lessler, MD: So with…it sounds like people are…recollect the discussion and have a sense of where the committee was at and I think probably what would be most helpful at this point is that if we could probably just put that in a formal recommendation. So is there…and this would be specific to Ticlodipine and whether or not we have a recommendation to its being on the PDL or not. So is there, you know…

T. Vyn Reese, MD: I'll move that Ticlodipine not be placed on the PDL secondary to safety concerns.

Dan Lessler, MD: Siri, you're…

Siri Childs, Pharm D: I didn't here it. I'm sorry.

Jeff Graham, MD: I move that Ticlodipine not be placed on the PDL due to safety concerns.

Dan Lessler, MD: Is there a second?

Robert Bray, MD: [inaudible]

Dan Lessler, MD: Any further discussion? All those in favor say, "Aye".

Group: Aye.

Dan Lessler, MD: Opposed? Okay, so the motion passes. Next we're going to review the medicines for ADHD. I wanted to point out that our discussion is actually going to be restricted to those medicines that actually have an FDA labeled indication for use in ADHD. So that would be…if you look at the list of medicines that were included in the review specifically the stimulants and the one non-stimulant, which would be Atomoxetine or Strattera. So that's what we'll be restricting to those agents with respect to safety and efficacy for ADHS.

Is…are our folks from OHSU on the phone?

Jeff Graham, MD: I'll call them.

Dan Lessler, MD: Okay.

Jeff Thompson, MD: Dr. Lessler?

Dan Lessler, MD: Yeah.

Jeff Thompson, MD: This is Jeff Thompson. I just want to make clear on the motion that this went through. So I just want clarity for the minutes. This means that if an endorsing provider writes DAW for that particular drug, Ticlodipine that then does not apply because it is not on the preferred drug list. I just want to make sure that we're all in agreement for the record. When you say it's not on the Preferred Drug List therefore DAW endorsing providers do not apply.

Dan Lessler, MD: That actually would not be my understanding. My understanding is that if it's not on the Preferred Drug List then as…as we discussed I mean the way a provider can access the medicine is by writing, you know, if they are an endorsing prescriber is by specifying, you know, dispense as written.

Jeff Thompson, MD: So you're making it a non-preferred drug.

Duane Thurman: Right. This is Duane Thurman. And a reminder, please, say who you are and speak into the microphone for our transcript, but the issue is whether it is a preferred or non-preferred drug and that…

Dan Lessler, MD: And I'll actually ask to make sure that this was the impression of the group as well. PDL stands for Preferred Drug List. So if we're saying it's not on the

Preferred Drug List we're meaning it's non-preferred. Now I don't know whether that…

Duane Thurman: Right. And I guess to clarify it the way I understand your motion it is that you reviewed the drug as part of the class, that you have made it a non-preferred drug…

Man: [inaudible]

Duane Thurman: I'm sorry?

Man: [inaudible]

Duane Thurman: That it is a non-preferred drug that is on the list, it is subject to dispense as written for endorsing prescribers.

Man: Okay.

Dan Lessler, MD: That's correct.

Jeff Thompson, MD: I think we should change…this is Jeff Thompson. I think for clarity sake…I mean we always get his confused with what's the on Preferred Drug List. You have two options—preferred or non-preferred, but when you say, "Not on the Preferred Drug List," there seems to be confusion out in the community and so I would recommend that there be some clarity with that.

Duane Thurman: Okay. This is Duane again. It's an issue that…the point is that you did consider this as part of the review of the anti-platelet class and so it is part of the Preferred Drug List program. It is not a preferred drug.

Jeff Thompson, MD: That's correct.

Duane Thurman: Okay.

Patti Varley, ARNP: This is Patti Varley. I just want to clarify though in this point that that does mean if a clinician did decide and they were an endorsing prescriber that for whatever reason in their clinical judgment this was a drug they needed to use the could use the DAW?

Duane Thurman: Yes. Okay. Are we clear?

Dan Lessler, MD: Okay.

Jeff Graham, MD: This is Jeff Graham. Marion, did you just come on?

Marian McDonagh, Pharm D: I did.

Jeff Graham, MD: Good. Thank you. We're ready for you.

Dan Lessler, MD: Hi, Marion. This is Dan Lessler. Welcome back.

Marian McDonagh, Pharm D: Hello Dan.

Dan Lessler, MD: Hi. So we are teed up here with the first slide, the drug class review on pharmacological treatments in ADHD. You can take it from there.

Marian McDonagh, Pharm D: All right. Thank you very much. Okay, well, let's go to the next slide. Let's see here…the next slide…is the next slide you have search strategies?

Woman: No.

Dan Lessler, MD: It's the results overview 146 studies included overall.

Marian McDonagh, Pharm D: All right. I think there are some slides hidden, unfortunately, so the slides that are hidden are the ones that just go over our basic methods that are the same except that I did want to just point out a couple of few things of what we included in your review. So I'll just tell you about those.

So the populations were both pediatric and adult outpatients with ADHD. We also looked for ADD hyperkinetic disorder and minimal brain dysfunction. And the list of interventions was really long. I don't know if you guys already have that. We included stimulants, which were amphetamine mixture—Dextroamphetamine, Methylphenidate, Dexmethylphenidate, Modafonil and Pemoline. And we included non-stimulants including Atomoxetine, Bupropion, Clonidine and Guanidine and then all of the atypical anti-psychotic drugs.

Jeff Graham, MD: Marion, this is Jeff Graham. We have made a decision that we're only going to discuss the FDA indications for ADHD, which would be the stimulants and the one non-stimulant.

Marian McDonagh, Pharm D: Atomoxetine? Okay.

Jeff Graham, MD: I mean you can go on and give the results for the rest, but for our discussion today we're not going to be discussing them.

Marian McDonagh, Pharm D: Well, that helps. I want spend time on those slides then other than briefly mentioning them. Okay, so, yeah, I think we are ready to go right to the results then. So there were a lot of studies in this review. We had over 200 placebo-controlled trials. The approach we took with those is that they have been reviewed multiple times before and, you know, the reviews of those drugs indicate that they are effective, but there are also a large number of head-to-head trials. So we focused on those and we used placebo or other types of trials when there was a lack of evidence for a particular drug or a particular outcome.

So next slide. I have a couple of slides on some general comments about the body of evidence in…just to start with because it's really…this is a really important part of understanding this body of evidence. First, there were no effectiveness trials found and so the large body of evidence seems to be relating to short-term efficacy studies. There is a lack of consistency in the outcome measures used meaning that the scales that are used…there's a whole wide variety of scales that are used to measure outcomes in ADHD, but in addition even when these same skills are used across trials they are applied in different ways and reported in different ways. For example, some studies might report that the total score, change in total score, and others only reporting change in a couple of subscale outcomes from the same scale. The other problem is that they are in general are very small sample sizes in this…in these studies. Some studies with less than ten patients for example.

Crossover design is really common here and while that's not necessarily a problem order of randomization may effect those…order of randomization can be a problem in crossovers and there was only two studies that actually assess the effect of order of randomizations and, in fact, in one of those they did find an effect. So it's concerning that there are so many crossover designs in this report.

Very short durations and non of the trials was rated "good quality". Overall, the evidence in pre-schoolers and adults is very, very limited and the mean age of children that were studied across borders 8 to 10 years old. So for generalized ability further than just the age group there, in addition ADHD sub types are potentially important in terms of what the mix is in the studies and comparing studies across the report. But only about 25% reported the ADHD sub type prevalence rates, but none of them actually went so far as to analyze the effect of their particular patient mix. So given those proportions there the range of proportions of patients with each sub type in this study…the other point to bring up about generalized ability is that there is the variation of response based on severity of illness is not addressed at all in the study.

Diagnostic criteria was a concern as well. How were the children or adults diagnosed? A class of studies—72% used the DSM3 or DSM4 for their basic criteria, but they usually added on other criteria to ensure that the patient's had the disease they were looking for. But the implications of adding on different criteria is not really clear. So how does that change your patient population from one study to the next? Primary white boys were included in the study.

Going on to the next slide. This is a grid of the head-to-head trials and the abbreviations within the cells are "C" for children, "T" is for teens and "A" is for adult. So you can see that the majority of the studies are comparing one of the newer drugs to Methylphenidate immediate release and very few looking at other types of comparisons.

So, on the next slide the first comparison that I want to talk about is the Methylphenidate immediate release versus sustained release. I think this is an important one so I'll start here. There were seven trials and overall there were no differences found between the drugs, the formulations. The largest trial in the whole review was in this group and found no difference between Methylphenidate immediate release and the [inaudible] formulation, which is Concerta. However, in the adolescent population there was a small, single blind study of teens. It was looking at driving skills in a simulated driving situation. And this study did find that the extended release formulation was superior to immediate release at driving skills late in the day so 8:00 and 11:00 at night.

There were no differences in adverse events in any of the studies that actually looked at that and then we also found a couple of observational studies, database studies that looked at a 12-month period of time each and they were looking for primarily persistence rates, which they found that the extended release formulations had better persistence rates than the immediate release. One that compared three different extended release products found that those products resulted in a 140-day persistence rate duration as opposed to 103-day on average with Methylphenidate immediate release. One study also looked at visits for accidents or injury and those were fewer with Methylphenidate the extended release and the immediate release.

On the next slide looking at the comparison of two sustained release formulations there was a single study looking at Ritalin LA compared to Concerta, which found Ritalin LA superior to Concerta on a few of the efficacy measures, but we really felt that caution was needed in interpreting this study because of some particular features of the study such as using the SCAMP outcome measure, which has been criticized in the literature for not having a great enough sensitivity to differences over time. They also used the very unusual analysis. They looked at an area under the curve in the change of the scale scores at 4 and 8 hours and it was in a simulated classroom setting. So there are several things to note about this study that might make us be concerned about giving full weight to the study. There was no difference in adverse advents reported.

So the next slide looking at Dextroamphetamine verses Methylphenidate. This is where we have the largest number of trials comparing the same two drugs. They were all fair quality and indicated no difference in efficacy between the two drugs. Looking at weight loss there is some evidence that Dextroamphetamine might have a great problem with weight loss than Methylphenidate immediate release. However, four of the trials reported no difference and two trials reported that Dextroamphetamine did cause greater weight loss with differences of .7 and .97 kilos between the two groups at three and six weeks. Again, very short-term results.

Later on when we get to looking at the long-term observational studies we'll have more evidence on weight loss and also effect on height.

On the next slide we have just a couple of trials comparing amphetamine mixture versus Methylphenidate immediate release. The amphetamine mixture was superior on a few outcome measures, but again there's no clear evidence of superiority. One thing that I may have forgotten to mention early on is that one of the…another additional problem with this group of studies is that they do not identify a primary outcome measure, which probably has multiple concerns associated with it. One of which is that there are…the studies are not calculating sample sizes. So they are just putting together a small group of patients and doing some testing. So it's very hard to know whether we can trust the outcomes when they are significant or particularly when they are not significant.

There is…from this…one of these studies indicated that their twice daily dosing of amphetamine mixture led to higher rates of loss of appetite and sleep problems, but that was in comparison to the once-a-day amphetamine mixture.

On the next slide we had a single trial that compared three different drugs or formulations. One was the Dextroamphetamine immediate release and then the extended release Dextroamphetamine and Adderall. And this study found a couple of different results. In the morning the immediate release of Dextroamphetamine was superior to the extended release formulation. And in the afternoon the extended release formulation was superior to amphetamine mixture.

In this study there was transient weight loss that was greater with amphetamine mixture than either of the Dextroamphetamine formulations. As I listed there, there are also some concerns about this study. So probably interpret with caution for sure.

On the next slide just a brief listing of the other stimulants, which we really didn't find enough evidence to make any statements about. With Pemoline only poor quality studies were found. Dexmethylphenidate there were a couple of placebo controlled trials identified in the FDA documents, approval documents, but there is nothing published and there is an inadequate amount of evidence in those documents for us to fully assess and report on those trials to you. The Modafonil, again, only one small placebo controlled trial.

On the next slide looking at…those are all very short-term trials that we have talked about so far. So looking at the long-term effects of stimulants, the longer term trials of stimulants versus placebo we included here. So anything that was six months or longer in a placebo controlled trial or in a non-medication controlled trial we included to assess this particular…what is the duration of effect of stimulation? Do they maintain their effects over time? In this group of studies is the multi-modal treatment of ADHD study, which is known as the MTA study. This study found that medication alone or combined therapy, which was a behavioral counseling therapy combined with medication were superior to behavior therapy alone or to community care, which included drugs and whatever other treatments the physician wanted to prescribe. So those were inferior to the drug therapy or combined therapy, which was usually a higher dose than what was given in community cares. That was the biggest difference.

The MTA reported no deterioration over two years in the effect on the symptom scale measurements. We found three other studies…6 months to 24 months in duration that did find deterioration over time in the effect on symptom scale measures. In looking carefully at those studies…I think the reason that we found a difference there is the dose. That in the MTA they were using more frequent dosing and higher dosing. I think some of those other studies are just older and used older dosing methods. The new dose in the MTA trial was higher.

So since the end of the MTA trial they continued to follow up patients after they completed the trials. So they were no longer assigned to the original group, but for 10 months of follow up they continued to follow so far and they are continuing to follow those patients. They did show a decrease in the magnitude of effects over time on those symptom scale measures, but there was still a significant difference between the groups based on their additional randomization.

Looking at the next slide this is…Atomoxetine versus Methylphenidate. There was only one trial and we…this trial included both children and adolescents. There was no difference in efficacy between the drugs. Atomoxetine caused more vomiting and [inaudible] while Methylphenidate caused more abnormal thinking. I won't discuss the Bupropion results. And Clonidine is also one you're not considering. Right? So I'll just skip that.

On the next slide is just about the other atypical anti-psychotics so we'll skip that.

So now we're on the slide that introduces the evidence about adults. So treatment of ADHD in adults is actually much, much less study than we found in the children with only 22 placebo-controlled trials and only 3 head-to-head trials. As a basic statement we also say that these efficacy trials suffer from the same limitations of the studies in children in that they're short durations, small sample sizes, and some of the other generalized ability problems.

So looking at the stimulants we did not find evidence that one stimulant was more effective than another. Dextroamphetamine versus Methylphenidate both in the immediate release formulations…there was one small trial for six weeks in duration where the secondary outcome measures were symptom scales that we were able to include in the review and this trial only reported changes from baseline and didn't make direct comparisons between the drugs, but both drugs appeared to change from baseline to a similar degree.

In placebo controlled trials of these drugs in direct comparisons of response rates they look fairly similar. We have noted that there are some differences in how they define response across the trials. But I list these here because there are similar to what has been reported for children for Methylphenidate, which is in the 50 to 75% range. Based on those large numbers of placebo controlled trials.

On the next slide looking again at indirect comparisons for the other stimulants, again, simply looking at the response rates. Here we see the Adderall from the single trial response rate of 70% compared to Pemoline, which has lower response rates. We'll see that across the boards to adults that Pemoline seems to have a lower response rate than the other drugs.

So looking at longer term functional outcomes we did try to look…try to fill in the gap for longer term outcomes by looking up observational studies and what we found was a study, which was a 10 to 12 year follow up study of boys who had been prescribed Methylphenidate during the ages of 6 to 12 years old. They used a historical controlled group in this study, which is a group of patients from the same practice who were previously treated in the practice, but not treated with drug therapy. In other words Methylphenidate and other drugs were not being used at that time. So the results of this study showed that more males were living with a girlfriend or a wife, however, they had held their last job for a shorter duration and fewer males were currently receiving psychiatric treatment and these are all in comparison to those [inaudible] historical controls at 10 to 12 years of follow up.

Now in the next slide all three of these drugs, I believe, are not on your list of drugs to consider today. So I'll skip those.

So on the following slide we have again simply listing some indirect comparisons, some placebo controlled trials. So for Atomoxetine from a single trial we have a response rate of 52%. Again, within the range of what we have seen with other drugs and with drugs particularly in children. For the stimulants the range is somewhere…Pemoline, again, is lower, but the other drugs are within the 50 to 70% range. So they all seem to be fairly similar, but very difficult to make true and direct comparisons across these trials, again, because of these differences in not only patient population, but particularly in how the outcomes are reported.

So looking for some other types of outcomes we have some uncontrolled studies that reported different outcomes we might be interested in such as quality of life. With Atomoxetine there were two studies that assessed quality of life and one found improvements over time in the Atomoxetine patients, but in the other study this finding was not replicated. Evidence about other types of symptoms that are seen in the ADHD patients, adults with ADHD such as depressed mood, anxiety

and changes in cognition…the results…the data here are really not compelling and we're not willing to make any statements on efficacy on those outcomes.

So looking at adverse events the…this slide is actually looking at three drugs for non-stimulants that you won't be considering. So if we just look at the right hand column these are looking at the stimulants, Dextroamphetamine versus Methylphenidate and again we did already find that there was no difference in the adverse event rates between those two drugs in particular in the head-to-head trial.

Moving on to the next slide. This is indirect comparisons of short-term adverse events particularly looking at insomnia, appetite loss and withdrawal rates due to adverse events that is. So looking at Atomoxetine the difference was compared to placebo was statistically significant for all three of those outcomes. And with the amphetamine mixture it was not significant based on insomnia, but that is…the difference there is actually quite large so it probably is based on the fact that there is such a small sample size in that study—only 27 patients. If you look at the rate of insomnia, 37% versus 20.8% in the Atomoxetine group it appears that the amphetamine mixture has a higher rate, but again it's difficult to make a direct/indirect comparison…or a direct comparison there.

The Methylphenidate immediate release…this trial there that is listed with 48 patients. The insomnia rates and the appetite loss rates are really quite high compared to other studies. So we think this study is probably a little bit different. It might be related to dose. It might be related to other factors in the study, but 63% of the patients in the Methylphenidate group had insomnia and that is quite high. A lot high than what is reported in the Atomoxetine or amphetamine groups.

If we move to the next slide we introduce the long-term safety at looking at observational studies. Our overall rating of the body of evidence for long-term safety is poor quality. That's because these studies really are not well designed. In both…not the [inaudible] well, but also the analysis is almost non-existent in most of the studies so they really are not very good. Very limited comparative evidence in particular. Only a few studies made any direct comparisons between drugs and indirect comparisons is extremely difficult again. One thing I wanted to point out is that there were…only one of these studies was reporting on adults.

So looking at the long-term safety of weight…effect on weight in children. Studies comparing Dextroamphetamine and Methylphenidate in both the immediate release formulations…both were associated with change in weight, which is actually failure to gain weight at the normal rate. Higher rates for potentially associated was Dextroamphetamine but there was a potentially difference in the relative dosing of Dextroamphetamine for any new studies. One of the studies that was five years in duration found that the difference in weight resolved after the second year of treatment. The non-comparative evidence is really not useful in terms of trying to make indirect comparisons. It is very inconsistent effects, which probably has to do with measurement—methods of measurement of weight and things like that.

On the next slide looking at a similar outcome—looking at height change in children. Again, comparing Dextroamphetamine and Methylphenidate the evidence here is more mixed. The methods of recording and measuring height are really quite inadequate. Neither of the drugs was associated with significant

reductions over five years in that one longer term study. Dextroamphetamine was associated with significant reductions over two years in another study, however. So a little bit of mixed results there and really, I think, for height…really I wouldn't be comfortable in making any strong statements about the effects or at least the difference in effect between Dextroamphetamine and Methylphenidate based on this evidence.

So looking at the next slide there is no comparative evidence for a variety of other important adverse events or safety outcomes only uncontrolled evidence. And then also we list there that there has been additional safety warnings added in the last several years to some of the products and I should update the slide Adderall XR was withdrawn from the market in Canada just for a short period of time and was introduced again to the market with additional warnings in the labeling. So it is just there for completeness.

Moving on to key question three in the next slide of looking at subpopulations. Looking at the issue of race or ethnicity…about half of the studies reported race or ethnicity data at all in their baseline demographics. Most of the studies were conducted primarily in white populations. We did find two studies that were conducted in populations that were non-white. One of them was a Methylphenidate study in African American boys. 75% of the subscale measure showed improvement. This is one of the definitions of response rate that has been used. So this does appear to be within the range of what…seen from the placebo-controlled trials in children. The other thing that was found in this study however is that…after controlling for other factors there was a linear increase in diabolic blood pressure over time in the boys.

A very small study of quantity in children in India – these children had hyperkinetic disorder and mental retardation and this study reported large improvements from baseline of 90% of the measures.

On the slide looking at [inaudible] race or ethnicity. New persistence rates looking at those two…one of those two observational studies of extended release Methylphenidate versus immediate release. The mean persistence rate with the extended release formulation was longer…or higher that is with ER than with IR regardless of ethnicity. So they were able to give an analysis controlling for ethnicity and found this similar results.

Treatment durations overall for the combined extended release formulations versus immediate release were lower overall among blacks and Hispanics compared to white children.

Looking at gender there have actually been a number of studies trying to look at the issue of, "Are there differences in response in boys and girls?" However, none of these studies were really very well done. They are usually comparing responses in a child that was previously done in boys to a small group of girls that were currently being assessed. But overall those studies found no difference in response rates between boys and girls. Looking at commonly occurring co-morbidities only half of the studies reported these co-morbidities, but none [inaudible] an analysis based on them. And again looking at the prevalence of these typical co-morbidities such as Oppositional Defiance Disorder. The prevalence in the study was 19 to 66% whereas the American Academy of Pediatrics estimates the prevalence rate to be 35% so it's within the rage for that particular disorder.

[inaudible] Disorder was a similar finding. The almost 26% is within your range as reported in the trials. For anxiety was similar, but for depression the American Academy of Pediatrics reports 18% of children have depression along with ADHD, but the trials only reported .7 to 6.6% so they were under represented in those trials. In adults for both Atomoxetine and Pemoline sub groups analysis of placebo-controlled trials suggested that the presence or absence of [inaudible] psychiatric illnesses did not alter the treatment effects. So there was some sub group analyses based on other types of co-morbidities there.

Looking at TIC disorder Tourette's Disorder in placebo-controlled trials Methylphenidate immediate release does not appear to increase over TIC severity or frequency. This was something that has been studied quite a bit with the thought that Methylphenidate actually caused ticks to worsen. So from the group of studies that are available it does not appear to be the case. I won't go over the quantity and data for you.

Now looking at mental retardation or developmental delay as the co-morbidity. Methylphenidate immediate release appears to be beneficial on most ADHD outcomes compared to placebo and there were six trials looking at patients with mild or border line mental retardation. Adverse events reported in this trials – scaring and social withdrawal occurred more often with the Methylphenidate than placebo.

On the next slide Autism and Epilepsy extremely limited evidence both relating to Methylphenidate immediate release, which was found to still be effective on ADHD outcomes in those groups.

On the next slide looking at substance abuse disorder, again, unfortunately, very limited evidence. Looking at the Methylphenidate immediate release versus placebo in adults our response rates of 77% in the Methylphenidate group compared to 21% in the placebo group was found in a trial of adults with cocaine dependence and again that 77% being within the rage, a little bit on the high end, but certainly within the range of normal response rates that we've seen across the trials. We did not find any comparative evidence on abuse or diversion potential related to any of the specific ADHD drugs. And that concludes the presentation of the report.

Dan Lessler, MD: What we're going to do now is just open it up to committee members to address any questions to you to clarify points and so forth.

Patti Varley, ARNP: This is Patti Varley. You made a comment about the Adderall controversy that occurred. Can you comment? Wasn't Cylert taken off the market in March of this year, as well?

Marian McDonagh, Pharm D: Yeah, you know, the…well, my understanding of what has happened with Cylert is the brand name has been taken off the market, but last time I checked there was still generic Pemoline available but that could have changed as well. I would imagine once the brand is taken off the market, the other would be as well. It has such an extremely low use over the years and also looking at the data you can see that it actually is not quite as effective as the other drugs.

Patti Varley, ARNP: And did your data reveal anything about the liver toxicity associated with it?

Marian McDonagh, Pharm D: It did not. No. One of the problems is that the trials are all so short, you know, some of them are a day long. So they wouldn't capture that. And then the long-term studies, the safety, there really were not any of Pemoline of any of these drugs that would be long enough to capture that type of adverse event. So they were dependent on numerator data such as the FDA med watch type of data.

Dan Lessler, MD: Other questions?

Angelo Ballasiotes, Pharm D: I was just going to make a comment. Angelo Ballasiotes with regard to Pemoline. It is my understanding that the manufacturer has discontinued. I think that is the generic manufacturer of the drug. Also, the hepatic toxicity is very severe with this drug and I think the literature shows or the package insert that they need to take hepatic tests every two months.

Dan Lessler, MD: Thanks. Alvin?

Alvin Goo, Pharm D: Hi, Marion, it's Alvin. Do you happen to know what the rate of the [inaudible] toxicity was Atomoxetine?

Marian McDonagh, Pharm D: No. Because there is no denominator data available. There are guesses, but it's really not adequate to know whether it is really real or not. From what the guesses are based on for instance number of prescriptions it would be very small. But I don't have the number for you.

Alvin Goo, Pharm D: Okay. Thanks.

Dan Lessler, MD: Other questions for…? Okay. Marion, we're going to…oh.

Andre Rossi, Pharm D: One question. This is Andre Rossi. The question is not quite related to the medication, but more to the treatment itself. I was just wondering if in your study did any of them show any difference in outcome of treatment adults who had a history of being treated during their childhood or their teenage years versus the adult who did not have any treatment in the past?

Marian McDonagh, Pharm D: That's a really great question and it is completely unanswered. Even though the trials of adults are much better quality than the trials in children they are again leaving out information such as that, which could really be altering the results of the trials as well depending on what the rates of adults in the trials who have been treated as children if there is any difference. But, no, these studies are not able to give us that kind of information.

Angelo Ballasiotes, Pharm D: This is Angelo Ballasiotes again. Is there anything in the literature with regards to head injuries and the treatment with these medications for ADHD?

Marian McDonagh, Pharm D: ADHD following head injury?

Dan Lessler, MD: ADHD following head injury?

Angelo Ballasiotes, Pharm D: Yes, yes.

Marian McDonagh, Pharm D: You know, none of…no, there's not. Not in the literature that we reviewed. I believe that there is some…more epidemiologic data about that, but it's not what would have been included here. It didn't have anything to do with treatment. So we don't have it. So I couldn't tell you anymore than that.

Dan Lessler, MD: You know, Marion, I wanted to ask. You commented a bit on persistence rates in the context of the study that was looking at differences by race and ethnicity. I was wondering if just generally if you could comment more broadly on persistence rates across the medicines?

Marian McDonagh, Pharm D: Do you mean trying to evaluate relative persistence rates across all the drugs that you are considering?

Dan Lessler, MD: Yes.

Marian McDonagh, Pharm D: Yeah. Unfortunately, we don't have more information. So for example persistence rates with, you know, Dextroamphetamine versus Methylphenidate we don't know. So what we have is simply the newest drugs compared to the oldest drugs and that's all we can tell you about persistence rates. So, right, if you're trying to let's say set up a grid of all of the different drugs and figure out how they relate to each other with persistence there is just a big lack of evidence.

Patti Varley, ARNP: This is Patti Varley again. You inferred this a couple of times and I don't know how the data all shook out, but the other question along that same line has to do with safety that you implied that the longer acting agents at least in driving records and in injury records indicated a higher safety record. So since one of our goals is to evaluate for safety can you comment on that?

Marian McDonagh, Pharm D: Sure. I think that that is true except that the evidence is so limited. So we have one observational study looking at, you know, visits to the ER or the physician's office for accident or injury and also one very small single blind study of driving using a simulator. So certainly the one, you know, the very, very small study using a simulator, that one, I think, is the weakest evidence. And the other one is slightly better. But overall it still is very limited evidence. So it's very possible that there is a difference there, but right now it's weak.

Robert Bray, MD: Excuse me. This is Bob Bray. My recollection of the California Medicaid data when you're talking about persistence rates seem to indicate not necessarily favoring a particular product, but that the longer acting drugs had a higher persistence rates than the immediate release drugs. Is that correct?

Marian McDonagh, Pharm D: That is true. If you…they also broke it down by drug and they did report a hierarchy based on the extended release products. But in general, you're right, their primary analysis was combining all extended release Methylphenidate products that were in their data set and comparing them to the immediate release and that is where they found the biggest difference by combining them.

T. Vyn Reese, MD: This is Dr. Reese. Do you think some of the persistence…this is just a comment, but do you think some of the persistence rates with the long acting formulation are just because parents only have to give it in the morning and don't have to give it also at school during the day, which is a really major problem with the short acting preparations?

Marian McDonagh, Pharm D: Right. And I think that that is certainly the argument, absolutely. And this data helps to support that argument.

Dan Lessler, MD: Is there any other questions from committee members or comments before we open it up to stakeholder input? Jason, are you still there?

Jason Iltz, MD: I am. I have nothing at this time.

Dan Lessler, MD: Okay. I just want to make sure because, you know, we can't see you. So we were going to open it up for stakeholder comment now. I have a…I've got a list here. I just want to make sure that everybody has had a chance to sign the list who wants to speak to ADHD medication. So is there…okay. And I'm just going to take it by order that people signed in. A few comments about this first. I ask that you limit your comments to three minutes and then also ask that you please identify whether you have any connection to pharmaceutical company at all whether you are here speaking on their behalf or sponsored in any way. And I suppose disclose any other potential conflicts. So first on the list, Jeff, did you have any other…okay. First on the list is Dr. Plonsky.

Marion, are you there?

Marian McDonagh, Pharm D: Yes.

Dan Lessler, MD: Great. I was going to ask if you could stay on until we're done because frequently there are issues that come up that we…in the stakeholder comment that we would like to sort of discuss with you. So I would appreciate your staying on.

Marian McDonagh, Pharm D: Okay.

Dan Lessler, MD: Thanks.

Carl Plonsky: Thank you. I'm Dr. Carl Plonsky. I work as a general pediatrician and a developmental behavioral pediatrician for the last 25 years helping these children who do need stimulant medication. I speak for all of the pharmaceutical companies in the past and no one in particular. That's who I'm representing today, but I'm representing the children who I'm caring for.

First of all I'd like to go ahead and say that each child and each family becomes its own study in the office. I would like to take you away from studies and statistics for just three minutes. And I would like to go ahead and tell you that in the office we have to deal with complexities of issues that studies do not address. We have co-morbidities that are unique for not just the child, but also for the parent. We have fragile families that can or cannot give medication once or twice a day in a reliable way. We have to titrate medicines to go ahead and address the child's appetite, when the parent wakes up, if the parent wakes up, and other kinds of issues that really are real life kinds of problems that make for either being effective or not effective. A long acting medication given an hour before a meal versus at the meal versus an hour after the meal can have a major difference in what a study sees. Certainly that's what see in real life in the office setting.

There are fewer physicians available to go ahead and manage complex issues especially with the black box warnings or the SSRI's and so these children are not being…are finding less and less help in the community. Compliance is a major issue. Duration of action is a major issue. I have some fast responders work Concerta 12-hour medicine for many children who go ahead and last four to six hours. On the other hand I had a boat builder yesterday come to me and say, "We've tried all the medicines, doctor, my 10-year-old girl is fragile

emotionally. She's got difficulties peer acceptance and with tears and Focalin extended release. It happens to be the best medicine and I can't explain why because all the other medicines didn't work. The day before that I had Focalin XR not working at all.

Research really shows differences in populations. They aren't differences in individuals. We need to have the freedom to go ahead and practice medicine in a way that is best for our patients and that is not often a reflection of what is in the studies. Thank you.

Dan Lessler, MD: Thank you. Next is Dr. Mandelkom.

Ted Mandelkom: Good morning. Ted Mandelkom. I manage a large adolescent and adult clinic for ADHD on Mercer Island. I've been practicing with ADHD for about 35 years. I had ADHD myself. I have a vested interest in these individuals and like Dr. Plonsky I am here…although I speak for all and have spoken for a number of the drug companies I am not here for any one particular company, I am here because I care about my patients and I've been doing this for many, many years and I've heard a lot of very good information presented but also I would like to state that much of the data presented has been very inadequate. We have diagnosed mostly small boys and most other information over the last 30 years is about small boys. We didn't even think this existed in adults until recently so we have very little information on women, girls and adults and we're trying to make medical decisions on treating a huge population with very little information other than the clinical information that we are gathering, which needs to be substantiated.

I would like to state that there is a reason why numerous drug companies are here and it's not because one company should be commanding the market. We have different groups of ADHD people out there. They clearly respond differently to different medicines. There is a group that truly likes Methylphenidate products. There is a group that truly likes amphetamine products and there is a group that truly loves the non stimulating Atomoxetine products. There are clearly going to be differentiated into Type I, Type II, Type III ADD. We cannot do this to the point that exist now and they all look like they are in the same bucket, but response wise or not. So as you saw in the slide 50 to 70% will respond to Methylphenidate with a good response. 50 to 70% will respond to amphetamines with a good response. Fortunately, it's not the response rate for the same people. So if you use both of those medicines you have a 95% chance, which is why I'm in business. I can get 95% of people better with relatively few side effects with one of the two groups of stimulant medications. They have been around for 50 and 70 years respectively and they have very little evidence of long-term safety problems. We lucked out because when we started using Methylphenidate and amphetamines back in the early days there was no data that it was so safe and we were purely lucky. But now we have many, many years of follow up, which we're trying to accumulate now for not just little boys, but everybody that documents.

So I'm here to plead for two things. Number one, please allow us to have multiple types of medications. Although the evidence may not be there the clinical evidence is clear that people respond differently to these medicines and truly prefer one over the other. Sometimes for therapeutics and sometimes because of side effect profiles, sometimes because of both.

I would like to please have long acting stimulants available, long acting products available. The short acting, which bounces people up and down like a ping pong ball is devastating. Not only do they not comply and take it, but they have rebound effects, they have appetite effects from the up and down quality of these short acting pills. The long acting pills have truly changed the treatment for these people and they are much happier. We still need short acting to fine tune morning and evening. So we can't be without that because these pills are anywhere from 9 to 12 hours long lasting and the day goes on sometimes for 16 hours in many of our patients. So we need to be able to fine tune them. The long acting really makes it much smoother and the more the long acting products become available, the better our treatment will be. I relate treatment of ADD with short acting like treating diabetes with short acting insulin. It would be ludicrous to treat all diabetics with short acting insulin. The long acting truly makes it better and of course to accomplish the best way to make…to regulate that for many of them.

So I really would like to continue to have all of the long acting preparations available. I would also like to point out that the safety factor for Adderall, although it was removed from the market, there was no valid evidence for removing it. It is now back in Canadian markets, thank God, because the kids up there were not able to get it otherwise and there is clear evidence that when you treat millions of people there will be some people who have adverse effects, [inaudible] effects, whatever, but it's not related to the medicine, it is the general background population that is showing this and they were able to determine this and realize that the medicine itself was not truly involved in creating a higher incidence of effects.

So I would just like to say we have millions of people that are undiagnosed, untreated. We are getting better and better products available. We need most of them and I hope you will be able to make them available to all of our patients. Thank you.

Dan Lessler, MD: Thank you. Dr. Gephart.

Harlan Gephart: Good morning. I'm Harlan Gephart. I come here today as a private physician to speak for the welfare of kids with ADHD. I have been involved with pharmaceuticals in the past as a speaker and medical consultant and am currently involved, but I'm also a Professor of Pediatrics at the University of Washington. I was also on the American Academy of Pediatrics Group that formulated the guidelines and I might say that I have read the Oregon State report, every page. As a matter of fact, there are issues in there that I won't comment upon at this time, but I would also commend to you the American Academy of Pediatrics, which was referred to in that document, which also did an extensive literature research by McMaster's University and a committee on ADHD by the American Academy of Pediatrics was represented by many different disciplines from all special…a variety of specialties including pharmacology, but also neurology and developmental pediatrics in child psychiatry. So I would recommend that guideline recommendations was in October 2001 in pediatrics and a supplement was just published in September 2005.

I want to make three brief comments. One about evidence-based research versus real life. I believe in evidence-based research. I teach it to medical students and residents. Unfortunately, we don't have evidence-based to cover every contingency in medical care. One of the things that is absent in evidence-based

research is something like compliance. It doesn't come up much. There has been an amazing improvement in care of children in the last five years as we have had available to us long-acting medications. It's no longer standard of care to give short-acting medications. In this regard rather than going to the evidence-based research, which doesn't give us that answer what we need to do is get expert opinion. And if you get expert opinion from people around the country like two you just heard from, Ted and Carl, who are trained developmental behavioral pediatricians who work with these kids, myself, child psychiatrist. I can give you hundreds of names, consultant with these people, ask them, "What would they choose to give a child with ADHD?" Overwhelmingly, they would choose to give a long acting medication. And I could go into many different reasons, but the biggest thing is compliance, schools sometimes now won't even give the medication. Parents have to come to school to give the medicine. You cannot manage a kid today with short acting medications. So we have to remember that.

The MTA study, which is referred to in the report is the most elegant study on ADHD that has ever been done. One of the things that the MTA study showed us is that the community group, this was all done on short acting medicine. The community group did not do as well as the research group. And if you take a research group and put kids in a closed environment like a lab school or a behavior class and have a research assistant give them a dose of medicine three times a day you'll get good results. If you send that same family home with a bottle of pills and say, "Take one three times a day." You won't get as good of results. The MTA showed us that. When I was a resident my colleague, Steve Dassell wrote an interesting article with Abe Bergman called the Half Life of penicillin. Everybody in this room has had that experience. If you give 10 days of penicillin to somebody for strep throat at the end of 10 days about a third of the pills are left. Why? Because we forgot to take all the doses. You can get away with that with a strep throat, but if you try to do that with ADHD…

Dan Lessler, MD: I'm going to have to ask you to wind up your comments.

Harlan Gephart: Okay. I want to talk just a bit about efficacy versus effectiveness. There is good effectiveness data. This study didn't show about it, but in substance abuse for example in the last five years look at the studies that Tim Willin(?) for example reported at Harvard looking at substance abuse in adolescence and the decrease in substance abuse if they took medications. You can't give adolescents short-acting medication. You can't run around with them and find them four times or three times a day, but you can medicate them on long-acting medication. So I think not to allow long-acting medications available for all patients, whether they are public or private would be a giant step backwards in the care of ADHD.

Dan Lessler, MD: Thank you. Next is Dr. Sumner.

Calvin Sumner: Thank you very much. It's a pleasure to be here with you especially following my friends and colleagues who are practicing treating ADHD. I'm a child psychiatrist. I've treated ADHD over 30 years and for the last 5 years my role has been developing the evidence base for Eli Lilly around the value of Atomoxetine and the treatment of ADHD. Probably the most important thing that I could stress to you is ADHD is not a simple disorder. It's a complex disorder and the most costly thing about ADHD is the failure to treat.

With full respect to the Oregon group who put together our very nice analysis of what we have in ADHD, treatments for ADHD or populations are efficacious. Treatments that are indicated for ADHD are safe. They have different safety profiles, but they are safe. One of the things quoted was the fact that most of the studies done in ADHD are done on a sanitized population. That means people who have ADHD only. The MTA study tells us that only 30% of people have ADHD only. The majority of people have ADHD plus some other disorder and that value and the treatment for whatever medication you choose varies depending on what other condition people have. In 34% of the patients in the MTA they had a co-morbid anxiety. The literature as published shows that Dopamine medications, stimulant medications, may or may not exacerbate underlying anxiety and may show inconsistency in the treatment of ADHD. In that population, that subset where a norepinephrine mechanism of action works differently, Atomoxetine has been shown to treat the ADHD and not make the anxiety worse. Similarly, ADHD in double blind placebo controlled trials has shown to treat ADHD consistently at the level of the people with ADHD only and not make ticks worse, not interfere with sleep onset in children and adolescents, not interfere with the trajectory of growth in three or overall long-term studies. So it really looks at the point of the fact that there is a domain of commonality amongst treatment medications for ADHD. And in that domain of commonality stimulants are excellent. And in that domain of commonality Atomoxetine is excellent. And they each have individual and unique aspects to them. Everyone treated for ADHD will have less of a risk of abusing substances in their life. Medications released into the public create a public health issue, though, for the potential of diversion. A medication that is non-abusable presents less of a safety issue around abusability.

So overall I would really commend to you to consider that the well equipped position for the most cost-effective treatment of ADHD will have at their access all of the medication necessary to treat all of the people with ADHD and not just the narrow subset of people who were studied in clinical trials with ADHD only. Thank you.

Dan Lessler, MD: Thank you. Dr. Staehli. Did I pronounce that correctly?

Christopher Staehli: I'm Dr. Chris Staehli from Behavioral Resources in Lacey. I moved to Washington about a year and half ago from Wisconsin. I've spoken for all of the drug companies and I'm not here sponsored by any drug company, but Novartis did tell me about this meeting. I was unaware of it. I was the largest treater of ADHD patients in the state of Wisconsin before moving here a year ago. I treat mainly Medicaid patients. What I want to say is…I've heard everyone here speak and I don't want to add to what they have already said, but I want to say that the number one thing that I do is treat non-responders. As you see, 30% of patients do not respond to whatever we choose. That's why I need flexibility. I use every single medication. They all work, they just don't all work for everybody. 10% of kids are super fast metabolizers just like people who drink four pots of coffee a day they take high doses of ADHD medications. I have one patient on 200 mg of Ritalin. I have patients on 160 mg of Ritalin. I have patients on 80 mg of Ritalin. I have patients on 5 mg of Ritalin. I have patients on 90 mg of Adderall. I have patients on 5 mg of Adderall. I need the flexibility. That's the number one thing I do is remove patients from medications. I get patients referred to me in the Medicaid population who are on Depakote, Lithium, Abilify and they have ADHD they were just never treated effectively and we need these medications to treat patients effectively. So what I tell parents

is, "I don't care what medication you choose, they all work, we just have to figure out what one works best." And 30% do not respond to whatever we choose. So we have to move on to the next one.

The advantages of Concerta, slow escalading curve, may last anywhere from 8 to 12 hours. All right? But may not, some people don't absorb Concerta. Ritalin LA, great medication, but only lasts about 8 hours. But if you're on Concerta, Concerta works, but doesn't last long enough, Ritalin LA doesn't last long enough. Focalin XR immediate release, sprinklable, last 12 hours. Adderall XR sprinklable, immediate release, 12 hours. You have to understand we have to treat kids who can't swallow medications. We have to treat kids who can't tolerate high doses, low doses, can't tolerate Adderall but can do well on Dexedrine and we need that flexibility. Any questions for me?

Dan Lessler, MD: Thank you. Matt Young from McNeil. Dr. Unis.

Alan Unis: My name is Alan Unis. I'm the Medical Director for Psychiatry at Sacred Heart Medical Center and I do as well speak for a number of the pharmaceutical companies regarding the agencies for attention-deficit hyperactivity disorder. I come to this…my present position having done in academic medicine for 20 years followed by a period of time where I worked within the pharmaceutical industry and drug development, but not on any agents that are related to the treatment of ADHD. My previous colleagues have said a number of things that I just want to echo. First, I want to congratulate the committee on the exhaustive review of drug studies provided by OHSU and reviewed by Dr. McDonagh. I also want to encourage that this particular committee review and integrate the American Academy of Pediatrics' principles for improving the physical environment for the provision of ADHD services. They had…there are four…and the reason I ask the committee to do this is because there are four over-arching principles in that policy that in fact many committees that are convened by various states to limit the list of preferred drugs are working across purposes to what is working within the field of pediatrics.

Those four over-arching principles include open access to appropriate therapy, consultative and collaborative services, eligibility of primary care clinicians to provide services for children with ADHD and their families, equity in financing the care for ADHD children and re-enforcing the best care for children with ADHD. As it relates to the medical treatments, the Academy asks for special attention to ensuring access to long acting preparations to limit the interference of treatment to the effected child's daily activities. And I would like to submit a copy of this policy to the committee if you would accept it.

ADHD really represents an entry level illness or subsequent chronic mental illness in the majority…in more than the majority of cases. Co-morbidities as we have seen have ranged from 30 to 70% for disruptive behavior disorders and substance abuse disorders with some indication in the research literature to support a preventive impact of appropriate treatment upon these co-morbid conditions.

Characteristics of the disorder place the effected child and adolescent at higher risk for accident related mortality and morbidity, which are mitigated by appropriate and effective medical treatments. And these treatments have to have efficacy that extend beyond the academic environment.

Non-compliance with treatment, in fact, as we've already heard from other colleagues here is global concern for all chronic illnesses and the more frequently a drug must be administered the greater the opportunity for it not being administered and thus to see under treatment. Children with ADHD are more commonly non-compliant than non-ADHD children. And the MTA demonstrated the superiority of consistently administered effective doses of medications. Once again these data support ready access to long acting medications, in fact, are preferable in the rationale treatment of children with ADHD.

I ask that the P&T Committee not limit access to long acting agents and that short acting agents may provide a rapid demonstration of efficacy, but in fact I would encourage the committee to develop algorithms to allow us to develop transitions from that short acting demonstration of efficacy to long acting agents to maximize long term treatment effectiveness. Thank you very much.

Dan Lessler, MD: Thank you. And finally, Peter Lukevich.

Peter Lukevich: Good morning. And thank you. My name is Peter Lukevich. I'm the Executive Director of Washington State Partners in Crisis at coalition of criminal justice interests dedicated to system changes in our criminal justice system as it relates to the treatment and incarceration of the mentally ill. I'm a former municipal court judge and a practicing attorney.

I wanted to encourage the P&T committee to embody, if you would, in your decision making open access to all forms of therapy and I do it for a slightly different reason because I don't have any of the clinical background or the medical information that was earlier shared with you, but from a criminal justice point of view we have a couple of concerns.

First of all, and let me point out that there are other state agencies who are watching what you do and taking what you do as some suggestions and leads for the way they will manage their prescription budgets and processes. With that said the criminal justice system shares populations between different penal institutions and different health care delivery agencies within the state. So, for example, the county jail prisoner who is being treated according to one formulary or one particular class of agent may pass to the Department of Corrections who in turn would have something similar maybe to what you're doing, or not, and then find themselves being discharged and ultimately going back onto a Medicaid role and being then treated in accordance with those prescription requirements. So because we share the common population in some instances, I would encourage you to provide as open and access to all medications, to all endorsing prescribers and for those…taking into account that those populations shift back and forth.

The other thing that I think is very important is that you consider definitely listing as a preferred medication a non-stimulant type of medication because of the increased aggressive and assaultive behavior that we find within our penal institutions and evidence that there is a tremendous black market available to the stimulant medications, which I'm not clinically taking on. They have their place and they are necessary, but when it comes to releasing a prison with a "supply" that they can then multiple by 10 and 100 times its value when you think about the cost of the pill, then the concern becomes, "What's the real cost of this treatment? What's it doing to us in other ways in the medical system including the emergency visits incarceration costs, prosecution, bail, jail and stigma, etc."

So I would ask you to look at that. And finally because I think there is pretty good evidence, and I think our friends from Oregon demonstrated that, that there is a new found body of information concerning adult attention-deficit disorder or ADHD. And as a result of not knowing what that means and what that population really is and thinking of it as either being undiagnosed or not diagnosed because of policy, I think we should be erring on the side of providing our physicians with all of the tools in the toolbox necessary to treat the disease. Thank you very much.

Dan Lessler, MD: Thank you.

Dick Miyoshi: I'm Dick Miyoshi from Harborview. I wasn't on the list.

Dan Lessler, MD: Afterwards if you want to just sign in, Dick.

Dick Miyoshi: Oh, okay. I'm part of the mental health…actually, I'm not actually part of the mental health work group, but I actually attend all the time. We were looking at pure ADHD, struggling with pure ADHD, co-occurring other disorders and mostly substance abuse because I work at Harborview and so we're wanting to open it up beyond stimulants. I mean we all know that ADHD drugs actually help decrease some of the problems of the co-morbidities, but we also have in real life many substance abusers that have the ADHD that are [inaudible] and so we would like to have other…the group would like to have other options whether it is Atomoxetine, Bupropion, [inaudible] is gone. Some of the tricyclic antidepressants. Some of the other antidepressants, which don't have the cardiac risk. That's basically what we would like. And as far as the rest of the stimulant group goes long acting, short acting, we're happy with that.

We have an ongoing struggle with the pharmacology versus the ADHD versus the co-morbidities and so on and so forth. This group will continue to research as much as we can and get the experts together to help us and to help you.

Dan Lessler, MD: Thanks.

John Dunne: I'm Dr. John Dunne. I signed up, but I must have signed up on the wrong list. There were four lists out there and so I'm on one of those lists, but not here. I'm a child psychiatrist. I'm in private practice here in Renton, but I've also been involved in ADHD over a long time. I chaired the American Academy of Child and Adolescent Psychiatry Work Group that created the practice parameters on ADHD. So I've had a long involvement with it. I won't reiterate the points that have been made before this. There is one additional point that I just wanted to add to this and that has to do with a long-term perspective on this.

What's been happening is that over the course of…actually, more than 20 years now we've been documenting an increasing rate or prevalence of ADHD, but also increasing rate of co-morbidity in complexity and severity. So that the kind of ADHD that we confront in our practices now is substantially more difficult to manage than it was before and that the addition of the long acting medications, not only the stimulants, but the Atomoxetine as greatly facilitated the whole issue of compliance, which was a major drawback to treating these children in the past. So I would just make those brief points just to add to that.

Dan Lessler, MD: Thank you. Is there anybody else that we might have missed? Okay, Marion, are you still there?

Marian McDonagh, Pharm D: Yes, I am.

Dan Lessler, MD: Thank you for staying on the line. What I want to do in a minute here, we're going to take a break, but while we still had Marion on the line I wanted to ask if for any of the P&T members, issues that were raised…sort of had raised questions that they wanted to address to Marion.

T. Vyn Reese, MD: Marion, this is Dr. Reese. You said there wasn't diversion…weren't any diversion problems that you knew of with these drugs. I'm concerned about the amphetamines, about diversion of amphetamines. Has that been a problem and reported in large trials or not?

Marian McDonagh, Pharm D: It is one of the comments that I think I should make for the Canadians. Our review is very narrowly focused on trying to find differences between the drugs. So, you know, evidence of that, a particular drug, particularly in this context is really difficult for us to say if there is something out there like might be in an epidemiologic report that doesn't identify what the drug is—that we might miss that because we're looking for a particular thing that we can compare the drugs to each other. So in that context we did not find any evidence at all about diversion. So, you know, we're doing the update of this report right now and we'll look again and look harder, but for a comparative report there is nothing.

Alvin Goo, Pharm D: Marion, it's Alvin again. For the non stimulants is there only one study with Atomoxetine and a stimulant and the Bupropion and the stimulant?

Marian McDonagh, Pharm D: Yes.

Alvin Goo, Pharm D: Or are there more?

Marian McDonagh, Pharm D: Um, well, there's one…

Dan Lessler, MD: Some differences and adverse events that...they were both more tolerability type adverse events and there were some on each side. That was [inaudible] versus methylphenidate. But Bupropion there were no differences. And, again, I think one of the problems with these is the [inaudible].

Other questions for Marion for clarification? Okay. Marion, thank you very much.

Marian McDonagh, Pharm D: All righty.

Dan Lessler, MD: I don't know...actually, Jeff...were you going to be coming back to join us later on? Or…

Marian McDonagh, Pharm D: I will be. I'll be back in the afternoon for the overactive bladder.

Dan Lessler, MD: In the afternoon, okay. Well, we'll talk to you then.

Marian McDonagh, Pharm D: Okay.

Dan Lessler, MD: And, we're going to adjourn here for just about 15 minutes 'til about quarter of the hour and then we'll reconvene to discuss the ADHD meds. The agenda has

been structured here such that I think that we have a comfortable amount of time to discuss what we've heard in terms of the [inaudible] presentation, stakeholder input and so forth. And ultimately come to a decision. So we won't have the time pressure that sometimes we've felt in the past. And I think in terms of how we've structured previous discussions, perhaps it's best just to begin with a conversation before we jump ahead to trying to put together any kinds of motions as people sort of begin to think through what kinds of considerations would influence a recommendation. So with that in mind, I was going to open it up to the P&T Committee members to feel free just to make some general observations and comments and then we can move the discussion toward an actual resolution. Jason, are you there? Just checking.

Jason Iltz, MD: Yes, I'm still here.

Dan Lessler, MD: Okay. Thanks. So, feel free, Jason, to jump in whenever. So, I guess, I'll open it up then to members of the committee in terms of thoughts they have as they're sort of contemplating how to put this all together.

T. Vyn Reese, MD: I'm Dr. Reese, and as a geriatrician, this is not my area. But I'm listening to the pediatrician and so I'm a good listener and I can study things, too. It's clearly [inaudible] both short and long acting. It needs to be on the preferred drug list, there's no question about that. It needs to be both short and long. They've made a compelling case for that. And the [inaudible], I've struggled with because of the diversion problem, but they are effective and may get another group of patients, so...we have other drugs on the [inaudible] too. So it's...that's probably not a good reason to leave them off. I'm concerned about Atomoxetine and the hepatic toxicity issue. I think that that's a drug that we probably maybe 2nd line in somebody who's an endorsing prescriber could prescribe that in a patient who was [inaudible] with the other drugs. But that would be a drug they probably wouldn't want to [inaudible] this. That's my initial take on it. And that's just from a geriatrician's point of view, the opposite end of the age spectrum.

Dan Lessler, MD: We have a couple people who specialize in psychiatric care, particularly of kids. So, Patti?

Patti Varley, ARNP: This is Patti Varley, and I would say your interpretation has actually been quite good. I would qualify a few things. I think that based on the data available, as well as the clinical experience of many people, is that the stimulants, short and long acting, of both kinds need to be available because there is clear evidence that there is populations where one is more effective than another. I think what you're alluding to is the other thing I think we need to discuss before we have a motion, which is are we discussing it in realm of pure ADHD, which is the first thing, or in regard to for instance co-morbidity. So if you look at having an ADHD person with a substance abusing history where you might want to use Atomoxetine or someone with a co-morbid anxiety disorder where you ma...how...does that need to be included in the motion or are we saying that that's a second line based on a clinician's judgment of beyond the ADHD piece what happens? But I would have to say, both clinically and evidence-wise, all of the stimulants, short and long acting, have equal safety and efficacy data. And in order to treat well you have to have the flexibility of having those agents available. The part for me, discussion-wise, when I look at the motion thing is the interchangeable part where it clearly in the evidence will say that if someone is a Methylphenidate responder they may or may not be an amphetamine responder versus a Methylphenidate responder, so that interchange part to me

needs to be discussed up front because I don't think it's appropriate to have interchange in them.

Dan Lessler, MD: I would say in a related way...just thinking back on the discussion around the anti-depressants is the issue if somebody is stable on a particular medicine. So this issue of somebody who is stable versus new starts, I think, is something else that you would want to be thinking about. Angelo, did you…

Angelo Ballasiotes, Pharm D: Yeah. Angelo Ballasiotes. My thoughts and another couple of points here. Diversion is not really an issue for kids the literature shows, it's not really an issue for kids when they get older. The issue may be with diversion with regards to the parents of the kids that is the medication. All of the concerns with regards to co-morbidity and this is a little big issue. I do treat a lot of people that have come out of prison and also that are in our county jail system. And these are people that have issues probably with ADHD that has never been treated. And they have gone along through the whole system for whatever reason and it has never been addressed, number one. And number two, have people with head injuries. We have ADHD secondary to head injuries. And, of course, we don't give them stimulants. We don't give them [inaudible] jail system and we don't give 'em stimulants. So we need to really address that population. I think that population is a lot larger than we understand. Empirically, this is what I'm saying. And you'll notice the [inaudible] on a national basis has nothing in it really. I've looked and have asked and things of this nature. There's not much information there. That's one of my main concerns. Or two of my main concerns.

Dan Lessler, MD: Alvin.

Alvin Goo, Pharm D: Hi, it's Alvin. Yeah, I think ADHD is really complicated and I think we just need better studies. The information we have right now sort of suggests that there is a lot of complexity, but it's difficult to determine who is going to respond to what agent and so it does seem reasonable to have two long-acting agents. Whether we have a non-stimulant, I understand the issues around adult ADHD in prison and I wonder if there's a system or a way that they can...if a patient has that, you know, your designated authorizing provider that he can just write DAW that will get filled as such. So.

Dan Lessler, MD: Bob, do you have any?

Robert Bray, MD: I think one of the...this is Bob Bray. I think one of the other things we need to keep in mind as we look at things, if we're going to start narrowing things down that we need to look at, and we don't have to look at FDA approval, we need to look at products that are available to both children and adults as we make those decisions. We may not get there if we're not able to really restrict things very much, but I think we just have to take a look at that too.

Dan Lessler, MD: Jason, did you have any comments or thoughts about those comments you're hearing?

Jason Iltz, MD: I don't know that I have anything to add other than I agree that treatment of ADHD is complex. I think it's one of those that it's hard to predict who will respond to what agent and so certainly trying to put together a list that provides opportunities for different agents is appropriate. At the same time, I do think that

we need to realize that the PDL is a list that's put together as a starting point and just because something's not on that list does not mean that it's not accessible.

Dan Lessler, MD: Jeff?

Jeff Graham, MD: This is Jeff Graham. I wanted to make a few comments. Dick Myoshi did speak. He's a member of a mental health [inaudible] group that Medicaid has put together to help them work through this whole issue around the preferred drug list and the different drugs that are used and patients that have problems in mental health. I think what we're seeing, and I'm an observer but I do participate in that group. The department has begun...they're taking their recommendations, they're putting together some indications for different uses of these drugs that they then approve them...it does require approval, some of those are on their expedited power of approval, but some of them are indications that they then use to approve those drugs for non-endorsing practitioners. And our group has done...already has done the drugs for depression and they're on their website, the indications for other drugs that are not on the PDL, and they've been working on this class. They're looking at the antipsychotics, which we haven't [inaudible] will be looking at. And also looking at...I don't want to go too far off, but they're looking at...we're going to be looking at the newer set of hypnotics and how they may be used in patients that have a diagnosis of [inaudible] diagnosis. So I'm very impressed with that group coming together with pretty good consensus about how maybe drugs that we don't [inaudible] for the preferred drug list, but there would be indications for those drugs by prior approval. And so what we've kind of said to them is that let the P&T committee work through this and then the agencies will work through what the recommendations are by the P&T committee and not to look so much at the comorbid conditions because that will be worked through with the agency, with the Medicaid...in their group of folks. So sometimes it's better not to let all the comorbid conditions start weighting you down as to how we're going to meet everything because that's sort of the job of this mental health work group and Medicaid. Does that help clarify anything? Or make it muddier.

Dan Lessler, MD: I don't know...I mean, I think it's great that that group's come together. And I think their work has been very helpful. I don't know the extent to which it helps in terms of our consideration of a recommendation here and sort of the factors that go into that. I wanted to maybe throw out just a...might be somewhat of an additional complexity into the discussion, but with respect to non-stimulants, I know it wasn't specifically discussed but was included in the review that we looked at as well as in the slides is the effectiveness of Bupropion as a potential non-stimulant, although not specifically FDA labeled. Certainly there is evidence of its effectiveness. I don't know whether that should influence our decisions or whether particularly, again, Angelo or Patti, whether you wanted to comment on…

Woman: Could I comment on that?

Dan Lessler, MD: Yeah.

Woman: Remember that Bupropion is a preferred drug…

Dan Lessler, MD: Right.

Woman: already in the anti-depressant class. So I think that there's totally free access to Bupropion and that you really don't have to consider it as part of the FDA labeled ADHD drugs.

Dan Lessler, MD: I'm thinking more in terms of concern that had been raised regarding...Sid Harris specifically was mentioning about his concern around liver toxicity and then there's been some discussion about but wouldn't you want a non-stimulant available and so forth. And that's the context in which I was bringing it up.

Man: [inaudible] as she points out, it's already...you know.

Dan Lessler, MD: Right.

Man: And so you can prescribe it and you don't have to say what you're prescribing it for. So it's open. It's available for people who need it [inaudible] ADHD. So it's not...you don't have to address that issue, it's already been…

Dan Lessler, MD: Patti, do you want to…

Patti Varley, ARNP: Well, I was just...because for me this is such a complex issue and listening both to the clinical evidence of all of my colleagues as well as the evidence-based data, which I agree, Alvin, is not...or whoever made the comment that we don't have it all yet, is a bit frustrating but we have a lot more clinical evidence of the complexity of this. And again, the hard part for me is thinking of it in its purest form versus in its real form. And I say that because it's hard to think of it as ADHD without thinking of co-morbidities when you look at the evidence based data that shows the percentage of co-morbidity with this disorder is so high. So I'm struggling as I'm thinking of this as, again, yes, I know Wellbutrin's already available. I know when and why I use it. But is this really more trying to leave it in that form with the understanding that both the other drugs on the PDL as well as the DAW allows us that second step into that. And what's my mission here is really what I'm trying to clarify. Is it to start at that grass roots of what is the evidence based for that diagnosis of ADHD and comment on that in here with the understanding that this is a diagnosis that is going beyond this first motion quite often because of the complexity of the comorbid condition.

Dan Lessler, MD: You had a comment [inaudible].

Andre Rossi: This is Andre Rossi. I was just going to reinforce that as Mr. Lukevich was mentioning in regard to other agencies are going to be affected based on this committee's decision, the Department of [inaudible] is one of them, and we need to make sure that we will emphasize on non-stimulants. And we have only one non-stimulant with FDA approval for treating ADHD, I would really like to have the committee to consider the Bupropion as another agent even though it is already on the PDL, but when it comes into our consideration, if the marketing is not in there for having the opportunity, it would be a disservice to other agencies who are going to be following the decision as being made here and convincing our psychiatrics in order to say that there is also another meds, a non-stimulant meds to be used in our type of a setting. If it comes from this committee here, we will be able to sell that much easier than if it does not come, if it does not mention at all.

Woman: I think I can help Andre and the Department of Corrections and maybe help your deliberations by saying that if you say that Bupropion is a preferred drug for

ADHD, okay, it is a preferred drug already so, you know, we would just leave it as a preferred drug but we could list it also as a preferred drug in this drug class.

Dan Lessler, MD: Other...any other…

Woman: Scratch that idea. It's not an FDA approved...yeah.

Andre Rossi: I realize that that it's not FDA approved, but haven't we gone the other way around for the other meds that we've selected in the decision making here for that they have not been having FDA approval but they have been commonly used for [inaudible]?

Patti Varley, ARNP: Well...this is Patti Varley again. When I'm listening to you say that the struggle I remember, and it may be incorrect, but the struggle I remember is that we haven't always had presented to us the evidence based data. And we've had on the committee people with clinical experience and we have struggled before where we didn't feel that really our mission was to look at the evidence and base our statements on the evidence taking into consideration our clinical experience. But that dance has been tough before and I'm not sure which way we've always gone, one way or the other. But I think that that is a struggle of when the evidence isn't there do you include it or do you know that clinically it is available under DAW. But is it part of your evidence-based statement that says the evidence is there to say that. I think we've struggled with that.

Jeff Graham, MD: This is Jeff Graham again. I do think that if we came to that and you needed that for [inaudible], Medicaid could bring that forward as a DUR issue, and because that way it's a...we're not going off what our recommendation now is that we want a decision made on the FDA indications for our PDL.

Dan Lessler, MD: Jeff?

Jeff Thompson, MD: This is Jeff Thompson. On the Mental Health Workgroup we are struggling with this and the same discussion came up; pure versus all in comorbid conditions. At least what we started the discussion it started to move it forward we started with the pure ADHD making decisions about how you look at it from a pure aspect and then see where the gap is. Because if you start mixing in you never really get to a discussion about where the gap is. And that's one of the things we're struggling. We will be bringing forward some recommendations for the February meeting on age dose for multiple use and those type of things and looking at practice variations, so you will see that.

Patti Varley, ARNP: This is Patti Varley again. As you said, the only thing I thought about in that mindset was, you know, new diagnoses. Quite often clinically that's where we begin too. We start off looking at the ADHD, trying to treat that, and through that is when clarification sometimes comes about co-morbidity. So in that respect it sort of maybe helped me a little bit in thinking if I'm thinking of a new patient walking in the door where that is the initial diagnosis I'm thinking of, that's how my treatment starts. It starts with the beginning of knowing what treats that disorder. If I uncover anxiety or I uncover depression, or tics, then I have to go to phase II. But maybe that's a way of thinking about it, too, as opposed to the patients that exist, which are much more complex because they've already been through that process.

Carol Cordy, MD: Carol Cordy. I wanted to...what Siri said about Bupropion and then changed your mind. If...suppose a patient comes in, you make the diagnosis of ADHD and for various reasons you want to start them on Bupropion. It's an off-label use. Pardon?

Janet Kelly: This is Janet Kelly. But when you prescribe Bupropion, most people do not write that it's for ADHD or it's for depression or whatever. And because it's on the Preferred Drug List, if you write Bupropion, they don't care what it's for you get it.

Woman: Which is just an odd quirk to this whole thing. Because...and I'm talking about this because of the whole Gabapentin fiasco that's been going on [inaudible], which we'll talk about later maybe. But suppose it weren't already available, you have no problem starting that for ADHD, is that right.

Woman: My other issue is my mission here is for safety and efficacy, and now I'm thinking if I put that on, I know about the seizure issue with Wellbutrin. That's a safety issue that isn't there...so my layers are getting heavier here as I look at the safety piece, which is the first word after evidence of safety. So, again, I'll just throw that into the pot.

Woman: And I think just looking at our form here, it would be complicated to put all three...or all three categories when you're saying they're equally...or are safe and efficacious, but no single medication is associated with fewer adverse events, which isn't true, and even the last part is the therapeutic interchange would be difficult. I think the first [inaudible], but the second two would be hard.

T. Vyn Reese, MD: This is Dr. Reese. I think we can just...the last sentence doesn't apply to this group of drugs. I mean, it just does not apply. I think we're sort of getting needlessly complex. I think...we should just do a baseline ADHD category and not [inaudible] all the co-morbidities at this time though in practice that's what happens. We need to have a simple, straightforward, you know, first tier type of drug category and not think about all the possible variations and complexities of providers based in practices. If you already have drugs on the PDL that cover those, than there's no reason to discuss that here.

Duane Thurman: This is Duane Thurman. I mean, make sure that you realize this is just a template. You guys can rewrite the motion any way you want. And I guess that the problem we have here is that we live and die by the FDA labeling. You know, we had situations earlier where we perhaps did not want a particular drug even available but the FDA approved the drug. So [inaudible]…

Patti Varley, ARNP: And this is Patti Varley again. Duane, and I was thinking about what was just said. You know, again, in my mission of safety, efficacy, etc., I just thought about, too, the drugs we could list that are FDA approved I would have to say Atomoxetine has a safety risk that the others don't, even though it's FDA approved. Do you know what I mean? So, yeah, I think we are challenged to look beyond the FDA label. That's what we're being asked to do. And so I think that needs to be taken into consideration.

Duane Thurman: Right. And I'm not saying that you can't do that, I'm just saying that you can't say...you can't dispense this drug under any circumstance.

Dan Lessler, MD: So it sounds like we're at a point where...in terms of trying to simplify this and think of what people count on and that we want; we want long-acting and short-acting stimulants, and we want both types of stimulants in both preparations that we think that it's important. Now, I think we're also saying in that that there's obviously not a lot of good, comparative evidence that individually each of these agents, both types of stimulants, long-acting and short-acting, have been shown to be efficacious and safe. So we can...and that the long acting of each and the short acting of each should be available, which leads us to Atomoxetine and how we want to think about that. There's been mention of just concern that it does have a safety concern that's not present with the two types of stimulants. On the other hand, it is a non-stimulant medication. So just as we're thinking in terms of long-acting and short-acting, it's important to have long-acting available. When we look at the non-stimulant versus stimulant, what...how do we want to come to terms with that, also incorporating into that the issues around safety.

Patti Varley, ARNP: So, you know, if I...this is Patti Varley again. If I can, again, think through it in my logic, it's that you list a motion with the stimulants first with all that you've included; short and long-acting of both types with the elimination of the sentence of interchangeable because they're not. And then a second statement about if needing a non-stimulant preparation then listing Atomoxetine there. That would, I think, cover all those bases.

Carol Cordy, MD: Carol Cordy. But you don't want to say it's as safe and efficacious say as Bupropion or…

Patti Varley, ARNP: Patti Varley again. You would have to make sort of this statement twice about safety, efficacy in special populations with stimulants and then a second one following that of non-stimulant where you would include the fact that it did have that side effect to be mindful of.

Alvin Goo, Pharm D: This is Alvin again. Do you want to either include a non-stimulant or...and leave that up to the DAW process, or should we include a non-stimulant and put a PA process under that?

Dan Lessler, MD: I think we can…

Alvin Goo, Pharm D: That's just a question. I don't know.

Dan Lessler, MD: I think we can either specify that a non-stimulant needs to be an FDA approved non-stimulant, needs to be on the formulary or on the PDL. I think that we can do, or we just are moot to that point and comment on the safety and efficacy of FDA approved non-stimulants.

Alvin Goo, Pharm D: I guess my issue with the non-stimulants is that there does seem to be some logic in that you don't want to be providing stimulants to adults with possible addiction, but in the same sense there's no evidence that giving somebody who has addictive qualities a stimulant versus a non-stimulant is any better. So that's where I am hesitant about the non-stimulant use because there is just not enough evidence to tell me one way or the other is it truly better in a comorbid population. It makes sense, but is it truly better. I don't know.

T. Vyn Reese, MD: This is Dr. Reese. I'd be concerned about Strattera in this population if you're talking about adults, among those patients who have addiction potential also have [inaudible] and so it may be not the drug of choice in those patients. So it's a

safety concern that needs to be addressed and we need to think carefully about how we phrase that and whether to include it at all.

Robert Bray, MD: This is Bob Bray. I think what we're doing, though, is really not providing an algorithm of how people should treat ADHD, which would be very complex. I think what we...I think should be doing is trying to address what do we think should be made available for physicians to do that informed consent process with the patient and be able to arrive at a reasonable conclusion. I don't argue the issue about the safety concerns with Strattera, but we also have evidence that says we don't even know what the risk is. It's a very rare, apparently asynchratic reaction. So I would prefer to leave the risk of that between the prescriber and the patient and not feel like through this deliberation we have to save patients from a very rare risk that really ought to be discussed by the prescriber anyway. So even though I agree with what Alvin said about, you know, we don't have evidence that Atomoxetine would be better than something else, I think that for the comorbid issues that have also been brought up, that's what we do in the informed consent process is try to look at relative risks, relative benefits, making an agreement with the patient based on comfort level and then following the patient. So I think that what I would like to see us do is to be sure that we include Atomoxetine availability because of the fact that there are going to be patients where I am not going to be comfortable at all prescribing a stimulant because of the risks that go beyond the usual adverse consequences.

Dan Lessler, MD: Other comments with respect to...it sounds like we've pretty much sorted through the stimulants and we're just trying to come to terms here with the non-stimulant. Yeah, please.

Robert Bray, MD: Bob Bray again. I think the one thing...you know, we've talked about stimulants as being in two groups and I think what we're talking about is methylphenidate and the amphetamine drugs. And then that leaves two other drugs that are sort of still stimulants but not within those subclasses, and that would be the Dexmethylphenidate and the Modafonil. So you know, those are other drugs in the stimulant class that don't fit into the subgroup that we just talked about.

Patti Varley, ARNP: This is Patti Varley again. I would say the two I would have listed was Modafonil and Pemoline. And I would have let Dexmethylphenidate be part of the Methylphenidate group.

Dan Lessler, MD: [inaudible]?

Man: Well, I do think that Modafonil does not have an indication for ADHD. So I'm wondering if [inaudible].

Patti Varley, ARNP: [inaudible] coming, but we don't have it yet.

Angelo Ballasiotes, Pharm D: Angelo Ballasiotes. Pemoline probably could also be excluded.

Dan Lessler, MD: So it seems like maybe we've gotten to the point, I'm wondering if somebody would like to make an attempt...and actually, Patti, you were doing pretty well here, at crafting a motion [inaudible] and people can…

Patti Varley, ARNP: So make a first attempt.

Dan Lessler, MD: First attempt. And people, before we before we have anybody second anything, folks can help you with it.

Patti Varley, ARNP: Okay. This is Patti Varley. I will attempt the motion. After considering the evidence of safety, efficacy and special populations for the treatment of Attention Deficit Hyperactivity Disorder, I move that...well, this is where I'm struggling. Do I just say methylphenidate based and amphetamine based agents of both long and short acting formulations…

Dan Lessler, MD: You're on a roll.

Patti Varley, ARNP: are safe and efficacious. No single stimulant medication is associated with fewer adverse events in special populations period. And no interchange. Now, in my wish I would go on to now say...and this is what I'm struggling with, I would like to include Atomoxetine as an option.

Dan Lessler, MD: Actually, before you go there, I was wondering if you wanted to comment…

Patti Varley, ARNP: [inaudible].

Dan Lessler, MD: Right. I was wondering if you wanted to build into the motion at this point a recommendation that the long-acting preparation of both types of stimulants be available.

Patti Varley, ARNP: [inaudible] I said that.

Dan Lessler, MD: Oh, did you say that? I'm sorry.

Patti Varley, ARNP: Both long and short-acting forms.

Dan Lessler, MD: Right. But you said now...you have said that they're both safe and efficacious long and short-acting. I think we might want to specify that a long-acting...that both a long-acting and short-acting preparation…

Patti Varley, ARNP: I see what you're saying, okay. Right. I see what you're saying.

Dan Lessler, MD: must be available on the PDL…

Patti Varley, ARNP: Okay.

Dan Lessler, MD: of each type of stimulant.

Patti Varley, ARNP: Okay. So rather than should it should say must.

Dan Lessler, MD: Actually [inaudible].

Patti Varley, ARNP: Right.

Carol Cordy, MD: Can I just say...Carol Cordy. There's confusion with the PDL and the preferred drugs on the PDL. And I think what we're saying here is they should be preferred drugs on the Preferred Drug List. So you may want to say they should be preferred drugs on the PDL.

Jeff Thompson, MD: This is Jeff Thompson. It does lend a lot of clarity when [inaudible]…

Dan Lessler, MD: That's fine. The clearer the better.

Jeff Thompson, MD: You guys are becoming experts now, but for the neophytes out there…

Dan Lessler, MD: They should be preferred drugs on the PDL. On the Washington State PDL.

Patti Varley, ARNP: We're not doing it for the world? Put in preferred drugs.

Dan Lessler, MD: Should be preferred drugs on the Washington St...right there. Yeah.

Woman: And here's a po...and after the last sentence, do we need to state that they cannot be…

Dan Lessler, MD: I think that's a good idea.

Woman: subject to therapeutic [inaudible]?

Dan Lessler, MD: [inaudible] medicine [inaudible].

Donna Marshall, Pharm D: This is Donna Marshall. The stimulant [inaudible] drugs, you can't interchange them without a new prescription anyways. A pharmacist can make a generic substitution but they can't change…

Woman: A Methylphenidate for a Dextroamphetamine agent anyway.

Donna Marshall, Pharm D: No, federal law prohibits that. So interchange, you know, the way that we do the other medications is impossible at this point.

Dan Lessler, MD: You know, I agree with you that operationally that's the case. I think, again, going back to the principal of clarity, since this is sort of the way we've been dealing with this issue across other classes, I would prefer to personally just see us actually just state that the drugs can't be therapeutically interchanged, even though I know that…

Jeff Graham, MD: This is Jeff Graham. That also helps us because many physicians don't know that and so...a pharmacist does, but many physicians don't, so it really does help us. [inaudible].

Woman: And I guess, although I would doubt it would ever happen, is I wouldn't want [inaudible] the same methylphenidate group for them to be interchanged a patient was stable on one form of that agent, like an 8-hour versus a 12-hour or short-acting versus a long-acting.

Dan Lessler, MD: So before we tackle the non-stimulant, here Patti, are there any...and we don't have a final motion yet to second or anything, but I'm just wondering if people have any other refinements to this first portion with respect to the stimulants. Jason, are you sort of getting this okay?

Jason Iltz, MD: Once we get it to its inclusive form, if you could read it back, that'd be helpful.

Dan Lessler, MD: It sounds like there are no other editorial comments. This is how it reads currently then: Okay. After considering the evidence of safety, efficacy and special populations for the treatment of ADHD, I, that is Patti Varley, move that

methylphenidate based and amphetamine based agents of both long and short-acting formulations are safe and efficacious. A long and short-acting form of each stimulant should be preferred drugs on the Washington State Preferred Drug List. No single stimulant medication is associated with fewer adverse events in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington Preferred Drug List. [inaudible]?

Man: Yes, are we ready for a second?

Dan Lessler, MD: No. Actually, we're not. Actually, maybe...that might be a good idea if people...maybe we should do this as two separate motions, and I think that that is a good idea. So did you want to second this, Jason?

Jason Iltz, MD: Sure. This is Jason. I'll second that motion.

Dan Lessler, MD: Okay. Is there any other comment or discussion. Okay. I think we can vote then. All those in favor please say Aye.

All: Aye.

Dan Lessler, MD: Opposed [inaudible]. Okay. So we sort of have dealt with the stimulants and we need to talk about the non-stimulant.

Dan Lessler, MD: We can...I don't think there are any other comments, we just got to sort of come to terms with it. So, Patti, you were getting started, so I was going to see if you would be willing to continue.

Patti Varley, ARNP: Try this again.

Dan Lessler, MD: Yeah.

Patti Varley, ARNP: 'Kay. It's Patti Varley again for a second motion attempt. After considering the evidence of safety, efficacy and special populations for the treatment of Attention Deficit Hyperactivity Disorder, I move that Atomoxetine be available along with the previous listed stimulants...I'm struggling here…

Dan Lessler, MD: Maybe you want to just begin with safety and efficacy...just start with...because I think first you want to comment on is it safe and efficacious.

Patti Varley, ARNP: Well, that's...I think I have to say efficacious because of the liver part with the...again, I agree that the evidence is slim, I think, unfortunately the evidence is there and presented and it is a side effect presented with that medication that isn't part of the stimulant group. So…

Woman: [inaudible] is that what you're trying to [inaudible]?

Patti Varley, ARNP: Yeah. But we have evidence...we have the study that showed it was equally efficacious to the stimulants presented to us. But we do not have...we do have that report of the safety issue with it that we did not have with the stimulants. Be made available on the Preferred Drug List for the treat-…

Woman: Did we want it...did we want it...when you say available do you mean preferred or [inaudible]?

Patti Varley, ARNP: Be on the preferred...yes. Be on the Preferred Washington State Preferred Drug List, yes.

Jeff Thompson, MD: This is Jeff Thompson. For clarity on that statement of special populations, it implies that there is a special population, and just so that we're clear on what actions you would like us to take as far as prior authorization or expedited prior authorization, some clarity in that statement would help. Or you didn't want it preferred and that's it. But it implies there that there is evidence that there is a special population.

Dan Lessler, MD: Well, [inaudible]…

Patti Varley, ARNP: Which is [inaudible].

Dan Lessler, MD: I would take another interpretation, I guess. We considered whether there are special populations, but we're not stating that there's a special population for the use of that Atomoxetine, and I would not want us to do that. Does that make sense? I mean, I guess we consider the safety, too, but we're leaving that off.

Carol Cordy, MD: This is Carol Cordy. Did we want that on as a preferred drug or just available on the drug list as a non-preferred drug? I thought we were thinking it should be non-preferred drug.

Dan Lessler, MD: [inaudible]. I'm still really concerned about that drug. And it doesn't look like it's as safe as the others. And I think that Bupropion is a lot safer. And we can't say that. And I think if you put it here, if you put Atomoxetine here, you're going to encourage people to use it, I think. And I think it's a more risky drug and the stimulants are safer as first line drugs to treat this with. And Atomoxetine can be reserved for [inaudible]. Atomoxetine can be reserved for patients who need it and don't respond to the other first line drugs in selected groups. But I think that's the smart way to do it. But I have concerns about Atomoxetine from data that's been presented.

Patti Varley, ARNP: And this is Patti Varley. And I just comment to your comment is that I don't see Wellbutrin as any safer because it has a seizure risk that the stim...I mean, they all...the problem is that...and there's no...it's not FDA approved. Do we use it, yes. But again, it's in that second line thing. I'm struggling with the fact that this is FDA approved, that there is a need for people to have access within this population to the range of drugs approved for this disorder, and that although we can't include Atomoxetine in the same group as the stimulants because it has some differences, I'm still struggling with I would like it to be available in the same way the stimulants are. And my motion may not be stating that as well as I would...my intention is.

Dan Lessler, MD: That's, I think, what it's coming down to, Patti, for you is wanting this drug to be available on the PDL.

Patti Varley, ARNP: As a preferred drug or just [inaudible]?

Dan Lessler, MD: As a preferred drug that one does not need to write DAW to access this drug. It's what you'd like to go with this. Is that accurate?

Angelo Ballasiotes, Pharm D: This is Angelo Ballasiotes. I guess I go back to what Dr. Bray was saying that this is the relationship with the clinician and the patient and I think that's where the issue with the regards to the safety [inaudible] stand.

Man: I agree, but I wonder if by putting it on the PDL that we are stating that Atomoxetine is an agent that everybody should be placed on. And that by putting it on the PDL I am encouraging them...or giving them the okay that for all adults it's okay. Or for all patients. And I don't know if the evidence really states that it's any better or worse. And so I do have some hesitancy putting it on a PDL.

Dan Lessler, MD: As opposed to having it available DAW?

Man: A DAW or some sort of PA process. I just...that's where I'm struggling.

Janet Kelly: Janet Kelly. I can understand why you're struggling, but I'm really concerned that there's a big population that will be untreated if this goes through having to do a prior authorization, this, that and the other thing. And I think that that's a disservice as well. We need to really consider that. And I think that the safety...that there is a safety thing, and I think that by putting something on the PDL does not say that it needs to be a first line agent. I think we put lots of things on that, you know what, there's kind of a tier that you think about clinically. But it's really not our position to set up a whole treatment algorithm. That's well beyond the scope of what this committee can do.

Man: But I think by putting it on the PDL you are stating it's first line.

Dan Lessler, MD: You're saying it's available as...potentially as a first line, as a first line [inaudible].

Patti Varley, ARNP: Well, but I...this is Patti Varley again. I would argue that if you use that logic, and Wellbutrin right now is already on the PDL, there are clinicians out there, if they so chose in their judgment could write that as a first line drug right now even though we don't include it in the ADHD list. So it gets back to the fact...and I agree with you, Alvin, if I...that joke about if we could control the world. You know, I think we...we have in our hearts a mission that we don't really have, which is we would like to influence the safe prescribing practices of all of our colleagues out there as part of what we're doing. And I like that, but I'm not sure it's realistic. And on the other hand, I agree with Janet that I have to give patients and clinicians access to appropriately prescribing within their judgment for what they think is best for their patients. So it's a hard one, I agree.

Carol Cordy, MD: Carol Cordy. And I think in the other drug classes we've discussed this and we haven't. In one way we've maybe swayed people's prescribing this by putting it by the DAW, that little extra step they have to take, and maybe that's the way we educate people. So I would still vote for keeping this, since it's FDA approved, on the PDL but not as a preferred drug, which means we wouldn't have to have a motion at all. Right? 'Cause are they on...any FDA approved drug is on the PDL, is that right?

Jeff Thompson, MD: Well, I mean...this is Jeff Thompson. For clarity sake, is any FDA labeled indication for which a drug company has signed a federal rebate who do not have a formulary we must make that available. And you are correct, I think the dichotomous that we need to think about is what does an endorsing provider have

to do DAW or not DAW and then what will the non-endorsing provider have to do depending on where you put this material. I mean, that's really what you're talking about. And, as you said, the extra step with DAW and then the non-endorsing provider will have to follow this as a non-preferred agent and then will work with the mental health group to come up with some criteria for the non-endorsing providers.

Duane Thurman: This is Duane. I think that it's important...I know it's frustrating because you do sit as the Drug Utilization Committee in addition to the P&T Committee, but I think you do have to be careful when you step into trying to influence prescribing behavior. And I know...I understand the issue and you guys can do what you want, but I think that you have to...when you're in this role, you're just simply saying, here's what the evidence says and you're looking at trying to say whether it should be preferred or should be on prior authorization or something. That's not something that, you know, that...that's something that should be done at the departmental level. And I think that if you're saying we want a short and a long-acting and a non-stimulant, then I think you're talking about preferred drugs. And…

Dan Lessler, MD: I agree with you, Duane. I think the issue here is one of wanting to be sure that a drug that might be clinically appropriate is made readily available. And I think it's struggling with having, you know...as you say, whether or not we want to specify an FDA approved non-stimulant must be on the PDL. I think really that's where we're at right now.

Woman: I think the discomfort here is that because we are not sure that it's as safe as the other drugs we're taking it out and putting it somewhere else. Because we can't say these are all equally safe and efficacious, which is what we've done before. And that's just quite a dilemma is we don't want to put it with those other drugs because we're not sure it's safe. But we want it to be available, because for some people it may be safer.

Dan Lessler, MD: Or be more efficacious. So, I think we're at a point that...very good discussion. I think we're at a point where we need to sort of cast our votes as a committee in some sense. What I would say is that maybe we should...as you have, Patti, and you may want to craft this a bit more. But we want...we might want to craft this motion such that we're stipulating that a non...for all intents and purposes that a non-stimulant FDA approved medication needs to be on the PDL.

Patti Varley, ARNP: This is Patti Varley again. I move that Atomoxetine be a non-stimulant. I thought that maybe putting that in there.

Carol Cordy, MD: I want to do something really awful. I want to go back to the first motion that we already passed because it sounds like we're making...we're clarifying the stimulants versus the non-stimulants. So I think we may have to rewrite this just for clarity because we're saying after considering the evidence of safety, efficacy and special population for the treatment of ADHD with stimulant medications, I move that...dah dah dah… and then the next one is going to be that we want a non-stimulant medication to be available. Because this doesn't really say why aren't we putting Atomoxetine on here.

Dan Lessler, MD: I don't think we need to do that. I mean, it...you know, it says Methylphenidate based and Amphetamine based. [inaudible] motion, it's moot to anything having to do with non-stimulants. I think we're fine just dealing with the non-stimulants

and this motion definitely gets us where the consensus in the group was where we wanted to go. So I wouldn't reopen that.

Man: And I think it gives the agency sufficient direction to…

Dan Lessler, MD: So...comment.

Man: [inaudible].

Dan Lessler, MD: I think Patti was saying her assumption was in putting together a...it's a good point. That we were...in some sense, we must be talking about new starts if we're saying that they're not that they're not interchangeable. Wouldn't that be implicit in how you would have to [inaudible]…

Man: Under 6088 excluded drug classes, this is not a drug class that is part of that excluded class [inaudible] applies.

Woman: No, [inaudible] protection does not apply.

Man: Does not apply in this class.

Man: [inaudible] I'm just clarifying the point that [inaudible] brings up that there are certain classifications of diseases that [inaudible] and I don't believe that this one was called out in the legislation; depression, schizophrenia disorders as it relates to immunosuppressants and cancer. But ADHD was not called out.

Several: [inaudible].

Man: [inaudible].

Man: Again, I'm just stating what the legislation called out as [inaudible]. You can advise us how you want us to handle it in your motion as an advisement, as Mr. Thurman said, we just give you a template and you tell us...you give us advisement, we'll try and make it work. I just don't want to get the [inaudible] protection confused with under the legislation with what [inaudible]…

Jeff Graham, MD: This is Jeff Graham. DAW does apply to this class. So if somebody is on a medication that perhaps not become preferred, if you are DAW the patient gets it.

Man: Wouldn't the C3 schedule help us...or C2 help us in this regard because…

Nicole Nguyen: This is Nicole. And this class, I mean C2s, as a pharmacist cannot get a prescription for say Ritalin LA and they cannot fill a short acting. You know, they have to fill what's there or get a brand new prescription. That's the reason why interchange doesn't apply.

Man: And actually, if you weren't...for a drug that may not even be preferred, signed Dispensed as Written, I mean, I'm sorry, signed it substitution permitted, that can happen. So then the pharmacist would have to call the physician back and say, This cannot...you can't...this is not on the preferred drug list. If you want the patient to have it you've got to sign the DAW and then they would get it. So I mean, so it's...they would get the drug.

Man: So I guess we need to decide later on whether we're going to want to grandfather people that are stable on these agents or not. Because if we don't make that decision it sounds like they're going to have to get switched to a PDL drug.

Man: No, I just said if you're on DAW they would not be switched. If you're an endorsing practitioner.

Man: And if you're not an endorsing practitioner then we decided the drugs are not interchangeable so there would have to be some sort of discussion.

Man: Right.

Dan Lessler, MD: So thank you for brining up the issue. So the motion stands and in terms of there's no therapeutic interchange and because they're C2 drugs and stuff it should not be an issue.

Carol Cordy, MD: Can I...Carol Cordy. Can I just add a couple of words to Patti's motion? After considering the evidence of efficacy in special populations for the treatment of ADHD, I move that...maybe we say [inaudible] is the only one, the non-stimulant Atomoxetine be included as a preferred drug on the Washington State Preferred Drug List. I think that's what your intent was, right.

Woman: Say it again.

Carol Cordy, MD: I move that the non-stimulant Atomoxetine be included as a preferred drug on the Washington State Preferred Drug List.

Dan Lessler, MD: Jason, do you have a sense of where we're at here?

Jason Iltz, MD: I do. My only comment at this point is do we remain silent on the safety? Or as an educational tool do we include the concern in the motion in terms of…

Dan Lessler, MD: Do you have a proposal or a thought about that?

Jason Iltz, MD: Well, I just try to think about what we've done in the past and if there's a concern that could be communicated, you know, a decision it may increase the frequency of monitoring and, you know, better use of that particular agent. I don't know that I have a specific edition at the moment. But I guess my question is do we need to add that.

Woman: Can I make a comment?

Dan Lessler, MD: Sure.

Woman: You're putting this on because it's a non-stimulant.

Dan Lessler, MD: That's correct.

Woman: So why don't you say after considering the evidence of efficacy in special populations and the need for a non-stimulant for the treatment of ADH, I move that [inaudible].

Patti Varley, ARNP: I think...this is Patti Varley. I think that the way it's stated now with her putting in the non-stimulant, that covers that point. The point Jason's making, which is a

question do we need to put in there the safety concern we have about the liver toxicity as part of the motion or not, and that's the question on the table.

Duane Thurman: This is Duane. I guess, you know, again we're getting to that area of where it's an FDA approved drug. It may have safety concerns. It's on the labeling. I would encourage you to make no statement on it rather than [inaudible] positive statement relying on the physician's relationship with the patient…

Woman: And their knowledge of [inaudible].

Patti Varley, ARNP: And for all the other drugs you're not listing all the other concerns or things and safety concerns and [inaudible] tests. You didn't list it for all the...what do you call it, Statins.

Dan Lessler, MD: So the...I think, then, perhaps we could put this motion out there for a sec. I'm just going to read it one more time. After considering the evidence of efficacy in special populations for the treatment of ADHD, I...that's Patti, move that the non-stimulant Atomoxetine be included as a preferred drug on the Washington Preferred Drug List. So that's a motion that Patti Varley has made. Is there a second?

Man: I second.

Dan Lessler, MD: Okay. Is there any further comment or discussion?

Jason Iltz, MD: This is Jason. I think in the past, and I guess my question wasn't that we need to point out the safety concern, but we really did consider safety, efficacy in special populations, and then usually the second part of our motion is to say we've considered it to be efficacious and therefore we would like it included or we make the recommendation. So I think we do need to at least put in there that we've considered the safety portion of it. We may not have to say anything more than that. Does that make sense?

Dan Lessler, MD: Patti would you accept that potentially as a friendly amendment so we can say, After considering the evidence of safety and efficacy in special...so we can have that…

Patti Varley, ARNP: [inaudible].

Jason Iltz, MD: That I move that it is efficacious or you know…

Dan Lessler, MD: Right, so I think we...right. We took that as a friendly amendment and it currently reads after co-…

Patti Varley, ARNP: [inaudible] as a efficacious…

Dan Lessler, MD: So it now reads after consideration...considering the evidence of safety, efficacy in special populations for the treatment of ADHD, I, Patti Varley, move that the non-stimulant, Atomoxetine is efficacious and should be included as a preferred drug on the Washington State Preferred Drug List. Okay. Is that okay with you, [inaudible]?

Man: Yes, it is.

Dan Lessler, MD: Okay. So, that's the motion that we have in front of us. I think there might be some different opinions on this. So it might be best if we just went through and people actually voted individually. So, why don't we begin with you, Jason. How do you vote?

Jason Iltz, MD: Yay.

Dan Lessler, MD: 'Kay. [inaudible]?

Man: Yes.

Dan Lessler, MD: Yes. That's fine. Okay. Okay.

Woman: Can I abstain? Or do I have to vote?

Dan Lessler, MD: I guess...it's a matter...you can abstain, yeah.

Woman: Okay. I will.

Dan Lessler, MD: Okay. I vote yes.

Man: Yes.

Man: Nay.

Man: Nay.

Man: Yes.

Dan Lessler, MD: Is somebody counting? So it was…

Man: Six, two and one.

Dan Lessler, MD: Six, two and one. So the motion carries then. Okay. So...and I think that's all for our morning work. We can adjourn and we will be reconvening at 1:00. Thank you.

Dan Lessler, MD: Before we begin. And if we could bring up the first slide.

Jeff Graham, MD: I have several announcements. Wanted to say that this will be the last time that we meet at the Radisson. We understand that this is being torn down for the light rail station for the airport. So we will not be meeting here anymore. And we have made...we know where it's going to be...the next meeting is but...it's going to come out to you by email and all the stakeholders because we know where it's going to be but we can't remember. Okay. The other announcement is I wanted to announce that Doctor Cordy, Carol Cordy and Ms. Patti Varley have been appointed to three-year terms on the P&T committee for beginning in 2006. So we're glad they accepted those appointments and that's our appointments for this year anyways. It's great.

Dan Lessler, MD: Okay. Thank you. We're just waiting for the projector to boot up here.

Marian McDonagh, Pharm D: Okay. [inaudible] this update presentation would you like me to skip the previous information. [inaudible] there, but I can either briefly go over them or just go to the new material only.

Dan Lessler, MD: What I would say...you know, I think we have...maybe we could include those and just...and go through them quickly.

Marian McDonagh, Pharm D: Right.

Dan Lessler, MD: You could...even if just to put it up there, I think that would be helpful.

Marian McDonagh, Pharm D: Okay.

Dan Lessler, MD: Okay. And we're looking at the first title slide drug class review on drugs for overactive bladder, update No. 3.

Marian McDonagh, Pharm D: Okay.

Dan Lessler, MD: And you can take it from there.

Marian McDonagh, Pharm D: All right. Thank you. We go to the next slide. Typical [inaudible] strategy. Just [inaudible] that for the updates [inaudible] were conducted through the spring of 2005. Next slide is data collection and analysis methods. Now the next slide, inclusion criteria, the new drugs were added in this update are Darifenacin, Hyoscyamine, Scopolamine and Solifenacin. The next slide [inaudible] included outcome measures and it's not all inclusive. These are examples of the kinds of objective efficacy measures we were looking for. On the next page are the key questions. And the following pages are the results from the previous reports, [inaudible] included with 21 head-to-head trials. If we go to the next slide these are the results for the update search. We included 11 new trials; three of these were head-to-head trials. And the next slide evidence of comparative efficacy. This is from the previous report. So Oxybutynin versus Tolterodine, both in immediate release formulation, no differences were found here in efficacy measures. On the next slide Oxybutynin immediate release versus extended release or Tolterodine immediate release versus extended release. Again, no differences were found in these trials. On the next slide we have the first update results. In this update there was a new trial of Oxybutynin immediate release versus extended release. And unfortunately this version of Oxybutynin immediate release is not actually available in the US, but this does add to the four previous studies comparing immediate release to extended release. New reduction [inaudible] 24 hours, no difference between drugs. No difference between drugs. No difference in reduction in incontinence episodes. Quality of life was studied in this trial, and was improved with the extended release but it's implied that it's [inaudible] improvements were not seen with the immediate release but the data are not presented so we can't make a comparison.

On the next slide [inaudible] evidence from the previous report; Oxybutynin versus Tolterodine. So this is immediate release Tolterodine versus extended release Oxybutynin. The extended release Oxy was superior to Tolterodine in reducing the number of incontinence episodes per week and [inaudible] per week. In a trial of Tolterodine ER versus Oxybutynin IR there were no significant differences found on any of the outcome measures. On the next slide, the Opera Trial, which was the comparison of extended release formulations of Oxybutynin and Tolterodine; the primary outcome measure was [inaudible]

change in urgent continence episodes per week, and there was no difference between the drugs on this outcome or a number of other outcome measures. There was one secondary outcome measure where Oxybutynin was superior; the percent continent at week 12, with higher in the Oxybutynin group.

On the next slide, Oxybutynin transdermal versus immediate release, single trial here found no difference between those two drugs in efficacy measures. On the next slide, Oxybutynin transdermal versus Tolterodine extended release [inaudible] different outcome measures there were no differences between the two drugs. On the next slide, looking at Oxybutynin immediate release versus Trospium, no significant differences were found on the primary outcome measure or the other objective outcome measures. Physicians, however, rated Trospium as a cure in 29% of cases and Oxybutynin in 17% of cases.

On the next slide, another one of our update slides, so this is new evidence, Solifenacin versus Tolterodine immediate release, a single trial. It was Solifenacin 5 or 10 milligrams versus Tolterodine immediate release 2 milligrams twice a day. The primary outcome measure was reduction in the mean number of micturitions in 24 hours. And this study was designed to [inaudible] each of these drugs or drugs and doses to placebo and not to each other primarily, so the outcomes here of all three were better than placebo. And also the secondary outcome measured reductions in [inaudible] incontinence episodes. All of the drugs were superior to placebo [inaudible] Solifenacin both [inaudible] were Tolterodine immediate release was not statistically significantly better than placebo on the secondary outcome measures. The study did report what they called an exploratory analysis of Solifenacin versus Tolterodine. And this statistical analysis of Solifenacin 5 or 10 milligrams was superior to Tolterodine when used in episodes of urgency. And Solifenacin 10 milligrams only was superior to Tolterodine when used in primary outcome measure which was micturition...reduction of micturitions in 24 hours.

The next slide, the second trial of Solifenacin...head-to-head trial included in the review, this is Solifenacin versus the extended release formulation of Tolterodine and it's the Star Trial. Solifenacin 5 or 10 milligram. Basically the patient started out at 5 and could go up to 10 if inadequate response was achieved. So the results are combined for the 5 and 10 milligram, whichever dose the patient ended up on, versus Tolterodine extended release 4 milligrams daily. The trial was designed as a non-inferiority trial for the primary outcome measure. So the primary outcome measure was changing micturitions in 24 hours and no difference was found between the two drugs on that primary endpoint. Secondary outcome measures, however, if non superiority was found on that primary outcome they could assess for superiority on secondary outcome measures. [inaudible] episodes of [inaudible] there's no difference between the two drugs. Urgency episodes, urge incontinence, pad usage and also an outcome measure of perception bladder condition Solifenacin was superior to Tolterodine on all of those secondary outcome measures.

On the next slide we found more head-to-head trials of Darifenacin, Scopolamine or Hyoscyamine. And moving on to the next slide. This is from previous reports. A summary of the active controlled trials that were included in the report. I won't go over those because they're not very helpful for our purposes today. And somewhere on the next page is the summary of the non-drug therapy controlled trials, which again are even more difficult to make any direct comparisons from. We'll move on from that one. The next slide is from an

original report also, which is looking at all the placebo controlled trials of the various different drugs and formulations. And I suppose on this slide the only important thing to show...to remind you [inaudible] there were no differences between [inaudible] and placebo found.

On the next slide we found two trials of Darifenacin versus placebo. And Darifenacin 30 milligrams versus placebo in a very short trial, two weeks, this slide found that one time was longer than with placebo. And there was no different [inaudible] reduction in the number of micturitions per 24 hours. 30 milligrams is higher than the recommended dose for Darifenacin. The second [inaudible] we found was Darifenacin 7.5 to 15 milligrams versus placebo for 12 weeks and the change in mean number of micturitions for 24 hours Darifenacin was superior. The change in number of incontinence episodes per week Darifenacin was also superior.

On the next page, the next slide, we have an additional study that was brought to our attention by the company. The Darifenacin 3.75 7 milligrams and 15 milligrams versus placebo for 12 weeks. These were reported as mean change rather than mean. So they're more difficult to compare to the other...all the other placebo controlled trials where we have reported means. So slightly different. So you can see that the 7 milligram and 15 milligram dose were superior to placebo in reducing micturitions for 24 hours, and also in reducing incontinence episodes per week. And a comment in the report there is a table that all of the placebo controlled trials response rate and these response rates with Darifenacin are very similar to the others.

On the next slide we have placebo controlled trials. One very small trial of Scopolamine transdermal for two weeks. [inaudible] micturitions that Scopolamine reduced much greater than placebo. And this number is actually...97.5 is much higher than any of the other placebo control trial numbers. Scopolamine is also superior in improving nocturia, urgency and urge incontinence. Solifenacin 5 and 10 milligrams, there was one trial comparing Solifenacin to placebo and again it was superior to placebo and the numbers for this trial are also very similar...the amount of reduction is similar to what's seen for the other drugs in placebo controlled trials.

On the next slide this is previous summary of the evidence on adverse events. Longer term evidence is limited and still is. So the overall grade of the evidence is poor for long-term. Dry mouth is the most common reported adverse event for both Oxybutynin and Tolterodine. And the rates of this and other adverse events were similar for both of those drugs.

On the next slide, looking at longer term studies, there was one long-term comparative observational study of Oxybutynin and IR, which was Tolterodine IR. There was a higher withdrawal rate in the Oxybutynin group. At six months only 23% of Oxybutynin patients were still on the drug versus 32% with Tolterodine, which was significantly different, but both very high withdrawal rates.

On the next slide, looking at Trospium versus Oxybutynin IR, in a trial that was...had at least a year follow up, Trospium had lower adverse event rates than Oxybutynin, lower rates of dry mouth, constipation, slightly lower visual disturbance. The overall dropout rate was higher in the Trospium group due to adverse events, however.

On the next slide, summarizing short term evidence, the immediate release formulations compared to each other, overall adverse events and dry mouth rates were significantly higher for Oxybutynin and IR. Extended release versus immediate release and incidents of dry mouth were lower with the extended release formulations. And with transdermal Oxybutynin incidents of dry mouth were significantly lower than [inaudible] Tolterodine immediate release.

Going on to the previous summary on the next slide of short term evidence, Oxybutynin transdermal versus Tolterodine ER, there was again lower rates of dry mouth with Oxybutynin transdermal, but it wasn't significant in this study. There were much higher rate of overall adverse events for the transdermal formulation, however, due to application site reaction. And ER versus ER, Tolterodine had slightly higher rates of dry mouth than Oxybutynin and this was significantly different. The rate of severe dry mouth was greater with Oxybutynin than Trospium. Overall rate of adverse events was comparable.

And on the next slide including the new evidence, Darifenacin IR there was small study of Darifenacin IR versus Darifenacin ER compared to Oxybutynin IR. And this was a 7 day crossover study. And the primary outcome measure was looking at visual [unclear] point. And there was no difference between all three drugs in visual [unclear] points. Looking at a sub-analysis of the Opera Trial, Tolterodine ER versus Oxybutynin ER, looking at the CNS adverse events, they were not significantly different between drugs. And withdrawals due to the adverse events, although were different, they were so small in both groups, it was not statistically significant.

On the next slide, results the adverse events from the Star Trials. Solifenacin 5 or 10 milligrams versus Tolterodine extended release. There were significantly lower rates of dry mouth with Tolterodine, significantly lower rates of constipation with Tolterodine, similar rates of blurred vision and no difference in withdrawal due to adverse events.

On the next slide, this is the other Solifenacin versus Tolterodine trial. This is the immediate release formulation of Tolterodine. Again, here we have no difference between the drugs in dry mouth. And then for constipation there were lower rates with Tolterodine than either dose of Solifenacin. Blurred vision there was- Tolterodine was lower than the 10 milligram dose of Solifenacin. Statistically significantly lower. And there was no difference in the overall withdrawal rates due to adverse events.

So in the next slide it's a summary of withdrawal rates for the other trials for the trials of Tolterodine versus Oxybutynin and found fewer withdrawals in the Tolterodine groups. One of six trials of extended release versus immediate release formulations found significant difference in withdrawal rates with Tolterodine ER having the lower rates than Oxybutynin IR. The trial of ER versus ER formulations there was no difference in withdrawal rates. Transdermal Oxybutynin versus Tolterodine extended release there were fewer withdrawals in the extended release group, and again this is related to the application site reactions with transdermal Oxybutynin. In trials of Trospium versus Oxybutynin there were lower withdrawal rates in the Trospium group. And then with the new evidence Solifenacin versus Tolterodine IR or ER there was no significant difference between either groups in the dropout rate.

So moving on to key question 3 for sub populations, we really do not, did not and still don't have very much information about sub groups for this particular group of drugs. Previously we only had a subgroup analysis of women from one of the trials, [unclear] IR versus ER, however the overall results, the population from the original trial was primarily women to begin with. So the results are not different.

If we go to the next slide, we have a similar sub analysis from the object trial looking at women only and overall the results were very similar to the total trial population, which again was primarily women to begin with. Additionally, when you have a subgroup analysis this time of Japanese patients and looking particularly at health related quality of life as an outcome measure, comparing [unclear] extended release to Oxybutynin immediate release. And those of the drugs increased the quality of life compared to placebo, that there was no difference found between the drugs.

So, summary of the evidence previously, comparative efficacy of Oxybutynin versus Tolterodine head-to-head trials do not provide sufficient evidence with clinically significant differences between the drugs in either the immediate release, extended release or transdermal formulations.

And on the next slide, Trospium versus Oxybutynin immediate release. We took comparative evidence. No difference in objective outcome measures. Some subjective measures favored Trospium. And on the next slide for comparative safety Oxybutynin versus Tolterodine, short-term studies indicate that Oxybutynin does cause more dry mouth and overall adverse events. However, the withdrawal rates due to adverse events are not significantly higher in these short-term studies. Short-term studies indicate that immediate release formulations in general cause more dry mouth and more adverse events overall. Again, withdrawal rates are no different. And one short-term study indicated transdermal Oxybutynin has higher adverse events and withdrawal rates than Tolterodine and then there's also the observational study that indicated a higher withdrawal rate for Oxybutynin in 6 months compared to Tolterodine.

On the next slide, comparative safety, again. Oxybutynin versus Trospium. Longer term and short-term trials, one each only, indicated lower rates of dry mouth and withdrawal rates with Trospium. On the next slide a summary of comparative evidence including the new evidence, we've got new evidence for [unclear] found very limited placebo controlled evidence for Darifenacin. Again, only placebo controlled evidence was available for [unclear] in direct comparisons are not very easy to make, but it doesn't really show- it doesn't indicate that there might be a big difference looking at- indirectly across placebo controlled trials. There was no difference in adverse events in a study of [unclear] point controlled to Oxybutynin immediate release.

And on the next slide, Solifenacin versus Tolterodine, there is evidence that Solifenacin has superiority on some outcome measures compared to Tolterodine immediate release or extended release. They were not different on the primary outcome measure comparing Tolterodine extended release to Solifenacin. And Tolterodine ER and IR have better adverse event profiles than Solifenacin in both of those trials. And that concludes my summary.

Dan Lessler, MD: Great. Thank you, Marion. So, at this point I'm going to open it up to P&T committee members for questions that they might want to direct to Marion regarding her presentation.

T. Vyn Reese, MD: Hi, this is Dr. Reese, Marion. The question about the visual near point. Is that a surrogate marker for visual change or CNS effect, or what is that exactly measuring, and how can we interpret that clinically?

Marian McDonagh, Pharm D: Right. I think that they were trying to get at the blurred vision and [unclear] associated with the [unclear] side effect. So they- it was simply described as visual near point in the paper and it really was not very well defined or explained. But it was simply holding the paper and see how far- how close they could get before it would become blurry.

T. Vyn Reese, MD: And a follow up question is have there been performance studies done on these drugs against each other or by themselves as far as how they affect memory or other measures of CNS function?

Marian McDonagh, Pharm D: That's a really good question and we've looked for that this time. The question has come up multiple time about CNS adverse events. And I think the only thing we found this time was that report from the object trial looking at the subgroup analysis trying to look at CNS side effects. And they simply grouped them as CNS side effects. So it's hard to tell exactly whether that would include memory and cognition. I would assume it would. But I can't say that we have found anything that clearly identifies that for even one drug, much less comparing them.

T. Vyn Reese, MD: Thank you.

Marian McDonagh, Pharm D: Hm.

Dan Lessler, MD: Other questions?

Robert Bray, MD: This is Bob Bray. The other question I have is regarding safety of Scopolamine. We have evidence of efficacy on one small study, but did you have any other evidence of adverse side effects in that group, particularly cognitive or delirium?

Marian McDonagh, Pharm D: Mm hm. Again, that's a great question. In this trial, no, because it was so short. It was two weeks long. And it really was not- they weren't even looking for those kinds of side effects. If they were there they would have had time to capture those. So no, we don't have that kind of evidence from these particular trials. It's probably out there for other uses.

Dan Lessler, MD: Any other questions for Marion from the P&T?

Angelo Ballasiotes, Pharm D: Angelo Ballasiotes. These pharmaceuticals are usually used in older people and my real concern is possibly delirium in these people. It doesn't take much to create that type of a situation.

Marian McDonagh, Pharm D: Right.

Angelo Ballasiotes, Pharm D: And I guess it's unfortunate that we don't have a little bit more information, even case studies to show some of the problems that we have current.

Marian McDonagh, Pharm D: Yeah, see, we looked at- there are some observational studies that were done in, for example, nursing home populations, and the problem for us is that there are too many interventions going on to know whether to be able to include them here to say whether it was caused by a particular drug. So that was why we were unable to do that for these. And the other thing is that really the age that is included in most of these trials is really quite young.

Dan Lessler, MD: Other comments or questions? Okay. I think we can open it up for stakeholder comment here. And, Marion, if you can- well, actually, I think, Marion, we're- you're going to be doing the PPIs as well, right? No?

Marian McDonagh, Pharm D: No. Actually, Susan Carson will come on to do the PPIs.

Dan Lessler, MD: Okay. Then if you can just stay on through stakeholder just in case we have some questions to redirect to you.

Marian McDonagh, Pharm D: Okay.

Dan Lessler, MD: That would be great. Thank you. And, just to remind people, if you are intending to give stakeholder input, we'd like for you to have signed up. I'm hoping everybody who wants to comment on these medications has signed up. Also, again- so there are two people who have not- just- okay. Then we can add you at the end. Thanks. I wanted to, again, reiterate, that comment- please keep your comments to three minutes and please let us know if you have any association in terms of being sponsored here and other conflicts. Thank you. So the first person is Dr. Gasparich.

James Gasparich: Hi, I'm Jim Gasparich. I'm Chief of Neurology at Swedish and Providence Hospitals in Seattle and I thank the panel for letting me speak. I'm coming from the standpoint of a clinical practicing neurologist and I strongly feel that the panel should consider adding some longer acting drugs to the formulary. And I say that because I'm not arguing that the pharmacologic efficacy of Oxybutynin immediate relief is superior or Tolterodine other drug is different, I think it's the clinical situation, the clinical efficacy that really matters. And I think the problem with Oxybutynin and immediate relief is poor compliance. And I think there have been several studies showing that if you look at six months only about 18% of the patients will still take that drug because of significant side effects. I think the dry mouth side effect but also constipation. So it's like why prescribe a drug that the patients can't tolerate if you have better tolerated drugs. I mean, strictly from a clinical standpoint, not efficacy, I think they're equally efficacious, but I think the patients do not tolerate Oxybutynin IR. And so- and I think if you look at it, in the IR form, too, you're talking about a TID dosing oftentimes rather than a once a day dosing with all the newer formulations, I think it's tougher for the patients to take it that way. I usually- if I start that drug I start it at 2.5 milligrams TID, which means they have to cut the 5 milligram tablet, because I think they have overwhelming side effects if you start too high and you have to [unclear] them up and that's a problem. So I think that's another issue that's better solved with the once a day drug. I think the CNS issues have been looked at somewhat. – I know I have a short period of time. There is an article in the Journal of Clinical Pharmacology that looked at Trospium, immediate release Oxybutynin and Tolterodine to look at quantitative EEG findings. And they used Trospium because it's a [unclear], which they know doesn't get into the CNS. And the conclusion was that Oxybutynin IR does get

into the CNS significantly, whereas Trospium and Tolterodine do not. So I think in the elderly population, which most of these patients are elderly, I think you can help avoid that- about 60% of nursing home patients are already taking another drug with anticoenergic effect, so it's added on top of each other. So, I really think that if you probably looked at your endorsing providers and what they're prescribing, I think you'll probably see there's a great trend towards not prescribing the Oxybutynin IR but using Tolterodine or whatever else on there, and so I really think we need to consider changing. If you're asking about personal preference between newer drugs, I think they all work- I'd rather see any drug added to Oxybutynin IR because I think they're all superior. I don't think there's any question about it. Personally I think Tolterodine, since it's the most commonly used drug, and people are familiar with it from a clinical standpoint and the dosing, that would be my personal preference, but I don't think I'm here to really give personal preferences on that. But I think- I'd like you to think about some new drug in this category. Thank you.

Dan Lessler, MD: Thank you. Next is Dr. Modarelli.

Robert Modarelli: Just want to thank you for letting me speak here briefly. I'm a urologist, Bob Modarelli in Tacoma. And I do probably more welfare patients than anybody else. People come from Aberdeen and anyplace south up to me, so I'm very familiar with the problems and the need for medications of these patients. And I would only, again, echo what the doctor said before is that compliance is a major problem and the one day dosing that you get allows the patient to perhaps get back into society. That's always my goal. Why do you see so many welfare patients is because you'd like them to get back into society, and if they're going to the bathroom all the time they can't get back into society. That's their excuse. So with one a day dosing, even their short memories will help them. And so I think that's critical. And Tolterodine's been around probably the longest and most of us are familiar with it. The CNS side effects are something you can think about, certainly in older people. When you go to the nursing homes you see the problems that we have there. And since most of the people in nursing homes are on these drugs, I think that we should all consider putting a one a day dosage out. And again, I would agree that they're all- if you compare them head-to-head, they're all relatively equally effective, and it's just a measure of the dry mouth and how many other thousands of drugs the patients are on that are drying their mouth out. And as physicians all of us have to look at, you know, what are we prescribing patients when we hand out all of these different drugs. So, my plea is to let it be a little bit easier for the patients to take a few less drugs. And if we can put one long-acting one on, that would be excellent. Thank you.

Dan Lessler, MD: Thank you. Dr. Harris?

Kirk Harris: Thank you for letting me speak with you today. I'm- I spoke with you in June and there are a few issues that I would like to clarify. I'm a solo family practitioner from Olympia, Washington. The bladder spasms that cause the urinary urgency, which is the hallmark symptom of overactive bladder, occur in patients ranging from age 19 from 91, and this is from the Noble study of 2000. It also occurs equally in men and women with increasing prevalence as the decades go on. These one out of every six people are not only the elderly, but also are younger DSHS population patients, which the PDL is affecting. The Totarula study of 2001 showed safety in the elderly, because unlike generic Oxybutynin, extended release Tolterodine did not cross the blood/brain barrier, therefore causing less sedation, fatigue, dizziness and cognitive impairment,

which in some patients may lead to falls or fractures. Extended release Tolterodine is better tolerated resulting in better patient compliance, effectiveness and medicine effectiveness and patient lifestyle as was presented by the OSHU person. Extended release Tolterodine also has been shown to be superior to the immediate release formulation in the VanKerbrok study of 2001, also with fewer side effects. The current recommendation from this committee from the 3/17/04 P&T committee meeting simply says Tolterodine and Oxybutynin are safe and effective in the treatment of irritable bowel- sorry, irritable bladder without regard to special population. My suggestion for a new motion would be, quote "after considering the efficacy, tolerability and safety, I move that extended release Tolterodine is to be the preferred agent for the treatment of overactive bladder on the Washington State DSHS PDL. There is insufficient evidence available at this time to the committee to prove superior efficacy of other anti-muscarinic drugs. In conjunction with the above-stated motion, it is the committee's recommendation that practitioners use caution when prescribing all anti-muscarinic medications to the elderly." I got the wording from previous motions made from reviewing from years of other P&T committee motions. And I would be happy to provide copies of these words if you would like.

Dan Lessler, MD: Thank you. Dr. Harris, were you sponsored today? Or…

Kirk Harris: No, I'm not.

Dan Lessler, MD: Thank you.

Kirk Harris: May I give these to you?

Dan Lessler, MD: What are those? Those are the…

Kirk Harris: This is just- what I did was I looked at all of the previous recommendations for other classes of medicines and verbiage that this committee uses and evidence that we have and…

Dan Lessler, MD: No- I think…

Kirk Harris: Easy to just use this perhaps as a format to guide you.

Dan Lessler, MD: I appreciate the offer, but I think we're going to respectfully decline. Thank you. Next is Christopher Conner.

Christopher Conner: I'd like to thank the panel first for allowing me the opportunity to speak. I'm going to try to stick to my three and a half minutes but I'm going to have to use some notes.

Dan Lessler, MD: It's three minutes.

Christopher Conner: Three minutes. But I'm going to have to use my notes to keep me on point. I am a clinical pharmacist. I work for Pfizer. I'm a clinical education coordinator with them. First thing I'd like to say is, as mentioned in the evidence based review update, no other overactive bladder medication has been able to show superiority to Tolterodine LA or Detrol LA when evaluating primary efficacy endpoints. Second, I'd like to highlight the tolerability profile of Detrol LA as it compares specifically to Oxybutynin immediately release, which is currently the preferred agent on the Washington PDL list. As mentioned by the authors of the

evidence based review, when looking at head-to-head trial data, there's a tendency for Oxybutynin immediate release to cause more anti-muscarinic side effects when compared to Detrol, primarily dry mouth. Now the authors of this evidence based update- review update, used clinical trial discontinuation rates as their measure of the clinical importance of these adverse events. And if you read the exact verbiage from the update, it states here that six of the seven studies comparing Tolterodine to Oxybutynin in any formulation found a lower rate of withdrawal with Tolterodine and reached significant in four. So numerically in six of seven and statistically significant in four of those.

Now, while clinical trial discontinuation withdrawal rates are valuable, I think a more effective way to look at this would be to look- to look at this issue would be to look at persistent studies, pharmacy clinic studies and what those show. And in the one clinic's analysis that was included in the evidence based review, in the analysis by Lawrence and Colleagues, statistically higher persistence rates were observed with Detrol with patients taking Detrol when compared to patients taking Oxybutynin in immediate release. Now more in depth review of all the [unclear] literature would uncover a number of other studies, but these studies tend to show similar findings. The Lawrence and Colleagues Study just typifies the findings for the entire body of literature. So, that is while overall compliance rates are low, there is statistically higher persistence rates seen with Detrol LA when compared to Oxybutynin IR. And all this, I believe, is evidenced by the fact that this class represents a class with one of the highest endorsing provider DAW rates. So one wonders within this class if providers in clinical practice have discovered these things, that Oxybutynin IR does not represent a good choice for many of their patients. So in light of all of these data; the effectiveness, tolerability, clinical trial, withdrawal and persistence data, I would like to ask the committee today to consider adding Detrol LA as a long-acting overactive bladder medication to the preferred drug list. Thank you.

Dan Lessler, MD: Thank you. Next is Dr. Cooper.

Thomas Cooper: My name is Tom Cooper. I'm a urologist in Everett. I bring the committee no motions. I do bring them 30 years of frustration in dealing with overactive bladders. I will tell you that I believe that all these agents that you've seen summarized are effective in reducing bladder problems. The problem that my colleagues and I have with them is that we can't make people stay on them. They will not take their medicines. They become constipated, they have dry mouth, they have eye problems. We are dealing with a quality of life issue. Nobody dies any earlier, there is no mortality associated with urgent [unclear]. If we're trying to treat urgent [unclear] we need to treat not only the bladder but the entire patient. I urge the committee to remember that most of these patients that we treat are older people on many other drugs and most of these studies have been done on healthy, young volunteers without any drugs. We all know that there are many medications that have muscarinic side effects and when we add a drug like we've been discussing we're going to get more and more of the side effects. The side effects that I'm concerned with are the side effects of cognition, the inability for our patients to even take the drugs for more than two weeks at a time. I personally do not use Oxybutynin at all in new patients. If I have a patient who happens to be doing well with it, I will continue it. I urge the committee to look at the new classifications of drugs because these patients will take their drugs with a much higher degree than Oxybutynin and Detrol, the drugs that we've used in the past and have used so poorly for our patients. These

new drugs represent a distinct advantage to the urologist and without them for our welfare patients we can't offer them. Thank you.

Dan Lessler, MD: Thank you. Next is Leigh Platte.

Leigh Platte: Hi. My name is Leigh Platte, and I'm a scientific liaison to [unclear] Pharmaceuticals. And I'm here to give you some evidence that Solifenacin is worthy of consideration for your preferred drug list. The ultimate goal of therapy for clinicians is a happy, dry patient. The ultimate goal for the patients is not only to be dry but to lose that terrible sense of urgency, that sense of having a wetting accident in public. In our short-term, our 12 week trials Solifenacin at 5 milligram dose showed an 81% continence rate, and that was with a less than 11% side effect dry mouth. And, as you know, dry mouth is the most common side effect reported in this classification of drugs and the most frequent reason for discontinuation of the therapy. In our long-term studies, our 40-week open label extension studies, 81% of the patients were still on Solifenacin at the end of 12 months showing great persistence. The patients that were continent that came into that trial maintained their continence over the course of the entire calendar year. I think you're more interested probably in the results of the Star Trial. Star Trial was our direct comparison to- from Solifenacin to Tolterodine extended release. It's a non inferiority study design of over 1100 patients in 17 countries in 117 sites. We were able to prove the primary endpoint that Solifenacin was not inferior to Tolterodine extended release in relation to the reduced number of micturitions per day. Our secondary endpoint [unclear] superiority in episodes of urgency, urgent [unclear] over all [unclear], pad usage and increase volume voided per micturition. In addition to that 59% of the patients were continent on Solifenacin versus 49% on Tolterodine extended release. The patients' perception of their bladder was more improved in this [unclear] on the Solifenacin group.

So in conclusion, I think Solifenacin did a pretty good job of meeting the goals of the patient and the clinician in reducing the urgency, having a sense of cognance (sic), more than 50% [unclear] and tolerability and in persistence; 81% continued on for the one entire year. This could translate to the state for lesser costs of office visits and pad usage. And it achieves all of your goals. So I hope you'll consider it as an addition to your Preferred Drug List. Thank you very much. I appreciate the time.

Dan Lessler, MD: Thank you. Next is Dr. Frankel.

Jeffery Frankel: My name is Dr. Jeff Frankel. I'm a practicing urologist. I'm president of the Washington State Urologist Society. I'm not sponsored. My office is here in Burien, so it's nice and convenient. It's surprising, really, that we're still debating Oxybutynin immediate release versus some kind of long acting product. I think for the practicing physician it's a very rare prescription. The only patients that get it are if they're economically can't afford a better drug or they have been on it. It's rare for me to be able to push it to the level where the pharmaceutical studies are done. In other words, most of the studies are done at the TID dosing. That's almost clinically impossible. BID is about the best we can get. So I really think the committee needs to look at alternatives. Most of the products that have been recently discussed here are very good as far as efficacy and tolerability. I like some of the titratable products myself where you can maybe adjust the dose for the patients if you're going to consider that as an alternative. But I do think that there are some morbidities associated with overactive bladders. It's not

infrequent for me to see a patient that's run to the bathroom at night and broken their hip, which may lead to the subsequent demise of the patient. Nursing homes are always calling us; they're changing the sheets, they're buying the pads, they're spending a lot of money on incontinence. I think it's the second biggest reason people go into nursing homes because finally the sons and the daughters come home and their mother's room smells like urine and they finally have to take them somewhere. So this is a big problem. I think you would be best served by improving the formulary. Thank you.

Dan Lessler, MD: Thank you. Dr. Staeheli? Did I do that right? Is that- is there a Christopher Staeheli?

Female: Excuse me. This is the conference operator. Are we allowed to add anyone to your calls? I have a Susan Clarkson.

Female: Yes.

Female: Or do you want her to call you later?

Dan Lessler, MD: Yes. No.

Female: Okay. And if anybody else calls, should we go ahead and put them in without announcing?

Dan Lessler, MD: No, you should announce them.

Female: Announce each one, okay. Thank you.

Dan Lessler, MD: Thank you. I'm sorry. Is there a Christopher Staeheli? No. Then next would be Dr. Harris? Actually, I think- actually Dr. Harris already- signed up already. And then there was one other gentleman- right, who hadn't signed up that- if you could…

Andy Weis: I'm Dr. Andy Weis. I'm a clinical pharmacist. I'm a regional [unclear] scientific associate director with Novartis Pharmaceutical and I just wanted to clarify a point that was made about the lack that Dr. [unclear] pointed out of articles relating to the safety of the newer agents. We submitted, it was in our response to the Oregon Health Science University Center for Evidence Based Practice two papers, one of which was by Dr. Gary Kay, who is head of the Washington Neuropsychological Institute in DC, which talked about the pharmacodynamic effects of Darifenacin in healthy volunteers. Once again, healthy volunteers are really not the people who take these medications. The comparator agent within that was Dicyclomine. This is the reason we published article in the British Journal of Urology International just this past month. The bottom line was that based on the validated psychometric instruments that Dr. Kay and Keith Wesness used within this paper, Darifenacin did not affect cognitive, cardiac or visual function in healthy volunteers and concluded this profile may reflect its relative M3 receptor activity. Equally, there was a paper that was done that we submitted as well done by Dr. Lipton which talked about Darifenacin compared with Oxybutynin within [unclear] patient population. In this case the patient population was over age 60. And in that paper it did show that Oxybutynin did have significant cognitive deficits in the standardized tests that were used in that patient population. I'm not a psychometrist so I'm certainly not going to describe what those were, but the bottom line was that there are papers out there

that do talk about this and we're a little quite frankly shocked that they didn't make it into the paper, the review by OHSU. I have not seen that final review published on the website yet, but when we did submit those papers along with our response, those two papers do exist. And if the committee would like further clarification, I can provide that. Thank you.

Dan Lessler, MD: Thank you. At this point, that's all I have signed up for people who have indicated that they want to speak. Have we missed anybody? Okay. Then we're just going to ask if there are any questions or comments particularly for Marion from the P&T committee based on what we've heard. Any points of clarification?

T. Vyn Reese, MD: This is Dr. Reese. Does Marion have any comments on that last paper that was mentioned?

Dan Lessler, MD: Marion are you there?

Marian McDonagh, Pharm D: Yes. Yeah, I'm here. [unclear] reviewed the papers that were submitted and- you know, [unclear] inclusion criteria, so that's [unclear] in the report. [unclear] difficult for us to include any of this we'd have to look at other papers [unclear] inclusion criteria we'd need to go back and look at others as well and [unclear] want to suggest that the inclusion criteria be altered to allow these kind of evidence. But yeah, right now those didn't make it in. So, [unclear] response at this point, you know, I can look at that one again, but the first one with healthy volunteers would not make it into any of our reports.

T. Vyn Reese, MD: Right. Thank you, Marion.

Dan Lessler, MD: Other questions or- Siri?

Siri Childs, Pharm D: I'd like to clarify for the Oregon House Sciences that the OAB report, final report, was posted December 20th on the public website.

Dan Lessler, MD: Any other questions or comments for Marion from the P&T Committee? Okay. Marion, thank you very much.

Marian McDonagh, Pharm D: Okay. Thank you.

Dan Lessler, MD: Appreciate your being with us.

Marian McDonagh, Pharm D: Okay. Bye.

Dan Lessler, MD: Bye-bye. So, I think we can- we have a copy of the previous motion is included here. Where is- is that in the motion [unclear]? There it is. Got it. Thank you. Okay. So, people can actually see what the current- the motion that was passed at the last discussion that we had of these medicines. And so what I would do now again, and sort of consistent with how we've been working is just see if there are any sort of general comments that people would like to make as we begin to move towards a motion.

Patti Varley, ARNP: This is Patti Varley. As you- as I look at the motion page, I think the thing that I think you alluded to, too, was the concern we had about we actually tabled this discussion in June with the hopes that we would have more information about the question of cognition and that's part of what's on this particular template here. I

think it is more difficult that that's what we were hoping for and there isn't a lot available there. The only other comment I would make has to do with the fact that- you know, and I don't know if in the future we can look at this as the issue of where compliance falls in. I think it was alluded to in the previous discussion earlier today and I think it's coming up more and more commonly, which is an issue of there is this safety and efficacy part, but there is also this other thing, which is my way of saying the pills don't work in the pill bottles. Which is, you know, even if it's safe and efficacious, if somebody's not taking it it's not going to treat the problem. And I just think maybe in the future we need to discuss where compliance falls into our need to discuss things. Because cost ineffective if you keep prescribing a med that isn't taken. That's not cost effective either.

T. Vyn Reese, MD: This is Dr. Reese. Yeah, I share some of those concerns. I don't think we still have enough data on cognition. And plus the Medicare patients are now not going to be our concern essentially. So we're looking at Medicaid patients and they're going to be a younger group than what we previously had. So some of the cognition concerns are going to be less urgent. I think there's a case to be made for long-acting formulation for compliance, and so I think one long-acting preparation is probably a reasonable thing to put on our formulary if it's hard to take a drug that many times a day and be compliant, even if the drugs aren't indifferent. I don't see a lot of differences between the drugs based on these studies. And so I'm- it's hard to pick between them. I think that adding a long-acting formulation may be reasonable, but that would be the only change I would see making.

Donna Marshall, Pharm D: This is Donna Marshall. I just want to remind you, you still have about 25-30,000 retirees in the Uniform Medical Plan that are 65 and older with Medicare. So it's not no elderly population. There are still some to consider.

T. Vyn Reese, MD: Yeah, we [unclear] aware of that, thank you.

Dan Lessler, MD: Other comment? Alvin, I saw you- didn't know whether you had a thought. Bob?

Robert Bray, MD: This is Bob Bray. I think, you know, relative to what we looked at previously, we have more drugs on the list than we did previously. So I think that's the other difference. And I agree that from a side effect profile standpoint, a long-acting medication looks like it has advantages. The data's not great, but at least it is leaning that direction.

Dan Lessler, MD: Any other comments? So it sounds- [unclear]?

Male: Yeah. I just kind of wanted to echo that. Quality of life is a real big issue, I think. And the elderly people, central nervous system events. And also long-term care, you know, slipping and falling and starts a person's demise, especially the elderly.

Dan Lessler, MD: So it sounds like at this point I'm sensing a consensus towards perhaps some motion that includes comment on including a long-acting preparation. Jason, you there?

Jason Iltz, MD: Yes, I'm here.

Dan Lessler, MD: Good. I'm sorry. I just wanted to make sure. I don't know whether you had any additional comment as well.

Jason Iltz, MD: I don't have anything to add at this time.

Dan Lessler, MD: Okay. So I'm wondering if there's anybody would want to maybe put forward a- try and stab at a motion. It seems like we need to take into account the point that wanting to include a long-acting preparation, sort of specify that, as well we need to be cognizant that there are additional medicines on the- that have been reviewed and whether or not we want to comment on those as well. Bob?

Robert Bray, MD: Bob Bray. The- I guess the one thing that I think we need to be careful about is if we came up with recommendations that would allow a decision that would allow Scopolamine to be our choice I think would be bad news. And I think we all agree with that. So I think that even though there may be efficacy data that says that it may work, we've seen side effect profiles that say any transdermal preparation has high withdrawal rates because of side effects and they don't even talk about the side effect we're worried about with that drug. So I would- even though there's efficacy, I think safety would- in my mind, based on recommendations that come from years of criteria and so forth, that Scopolamine would not be a good choice to include with this category of drugs.

T. Vyn Reese, MD: This is Dr. Reese. I agree. I think the data on Scopolamine is pretty scanty and the drug has significant side effects and probably shouldn't be included in this list.

Carol Cordy, MD: Carol Cordy. I- just a point of clarification, I think the- and a question. I think those of us that have signed up to be endorsing prescribers sometimes forget that, you know, it's easy to write DAW but, I guess my two questions are, What is the actual process that a physician has to go through- because all these drugs are available on the bigger preferred drug list. And the second one is, At this point what percentage of prescribers in Washington State are endorsing.

Female: Okay. Right now our new drug…

Dan Lessler, MD: I don't think your microphone is on. Or it needs to be closer.

Female: Right now the new drugs that were not reviewed before are not on the Washington PDL, so they require prior authorization. So your motion, you know, whatever it is will include the new drugs, either as preferred or non preferred drugs. They will be part of the PDL because they have now been studied and they have been subject to review. And so if you're an endorsing prescriber and you're writing for any of these drugs on the PDL and you write Dispense As Written, you will get one of these- you'll get the drug of your choice. To tell you that the opt out- the DAW opt out, the gentleman was correct, this is the highest DAW opt out drug class for Medicaid and it is about 23%.

Carol Cordy, MD: And what's the process for the non endorsing prescriber goes through to get…

Female: Not endorsing prescriber would hit a hard stop, require prior authorization and they have to…

Carol Cordy, MD: And do you know approximately how many non endorsing prescribers there are? What percentage?

Female: Are- no, I don't know that. But I do know that the compliance rate in this class is about 80%. So, you know, 80% of the prescribers are using immediate release of Oxybutynin. But we do have like a 20 some percent DAW rate for- and it's usually for a longer active form.

Dan Lessler, MD: So, I'm wondering if somebody would want to just try and craft a motion here?

T. Vyn Reese, MD: This is Dr. Reese. I can go ahead and try to craft a motion. Again, cognition is a concern. We don't have hard evidence about cognition and the differences between all these drugs. We have some preliminary evidence but not a lot. So- but I still think a longer acting preparation needs to be added. So given that, After considering the evidence of safety, efficacy and special populations for the treatment of overactive bladder, I move that Darifenacin, Hyoscyamine- there's not much data on Hyoscyamine. I would like to delete Hyoscyamine. Oxybutynin, Solifenacin, Tolterodine and Trospium are safe and efficacious. No single incontinence medication is associated with fewer adverse effects in special populations. These drugs cannot be subjected to therapeutic interchange in the Washington Preferred Drug List. A long-acting preparation is to be included in the PDL.

Female: Did you say cannot?

T. Vyn Reese, MD: Cannot. It can't be substituted. The drug- the different, you know, chemical name drugs can't be substituted, not equivalent.

Dan Lessler, MD: You want to comment on your concerns about therapeutic interchange here?

T. Vyn Reese, MD: The dosages are different for different drugs and not exactly therapeutically interchangeable.

Janet Kelly: This is Janet Kelly. Vyn, I'm concerned that that's too many of the drugs that we do therapeutic interchange and that's where, you know, some of the pharmacy associations and others have put together some comparative dosing guidelines for the dispensing pharmacists. I don't think that just because 5 milligrams of this drug is not equivalent of 5 milligrams of that drug doesn't mean that they're not therapeutically interchangeable.

T. Vyn Reese, MD: I mean, if it's new starts it doesn't matter. If you're going- if you're switching from one to the other, if you're making them switch- you want to switch, that's a different thing. So I- it's- are there tables regarding that interchange for this class of drugs? I wasn't aware of that. I could be educated…

Dan Lessler, MD: Siri, did you have a comment? I thought…

Siri Childs, Pharm D: Well, my comment would be exactly what Janet said that the pharmacists know the equivalent doses for the long-acting versus the short-acting. So I think that they could do a [unclear]…

T. Vyn Reese, MD: That's a different thing. The drugs in the same- like Oxybutynin long-acting and short-acting were- Tolterodine long-acting and short-acting, they could be substituted because they're the same drug essentially and the same total

milligrams per day. That's a different question. The question is what do you substitute Trospium for Oxybutynin at a certain set dose, and that's a different question. I'm not sure that we've addressed that.

Donna Marshall, Pharm D: This is Donna Marshall. Currently the drugs that were previously reviewed like Detrol LA or Tolterodine are being interchanged with Oxybutynin IR, so this making them not subject to therapeutic interchanges is new for this drug class where they have been interchanged in the past.

Dan Lessler, MD: But I think, Vyn, to your point, they're new medicines that haven't- previously they were the only IR ER preparations of those meds are all at least considered, really, and now there are additional medicines that appear to be efficacious. So I think the question to be [unclear]…

T. Vyn Reese, MD: The question is if you have a written guideline on dosage substitutions, that's fine. It's not like it's not like you're going to have- I think- is there a certain accepted guideline that you have that you're working from now?

Female: There's not an accepted guideline that's written that I'm aware of, but you could argue that for all of the drug classes that we do interchange on. I mean, if there's a question about what dose the pharmacist should give, they could always consult with the prescribing physician. And that's kind of been our position all along. Again, I don't think that just because there's no written book that says, If this, then that, to- if that's going to be our argument, then I don't think we could interchange on any drugs that didn't have that same published table.

Dan Lessler, MD: Dr. Reese, I know before like on inhaled corticosteroids we had different drugs and different therapeutic interchanges based on the dosage and the potency. It was very clear cut and that's- we decided to do that based on the accepted standards for potency in that drug class. So that was my only question. I mean, I- you know, I'm not sure what you're saying. Are you saying that you could just go ahead and just change long-acting preparations for one for long-acting for the other and just, you know, what dose would you chose?

Female: Currently that's being done. If you have somebody on Tolterodine long-acting it's being changed to Oxybutynin immediate release. It's being done right now. I mean today. That does occur.

Male: But that's a start, though, isn't it?

Female: No. No, that would be anybody. Once we implemented the drug class that start- that, you know, started to occur.

Janet Kelly: Janet Kelly. I think the one thing that maybe is confusing, and just to put into perspective, when a pharmacist gets a prescription for that it's like no, there's not necessarily a guideline as to what you do, but myself I'm not really familiar with starting doses for some of these new ones. So I see what the dose is, I see what the dosing range is, and I'm like, okay that's a medium dose of this medication, I'll give them a medium dose of this one. Or it's a starting dose. That's how you typically would do that sort of a thing. It's not like you just blindly say, I'm going to do this. You kind of- there are recommendations as to what the starting dose is and what the range is. And you look at the drug that was prescribed versus the drug you're going to switch to and you kind of [unclear] with where in

that range. That's kind of the practical thing how I would do it, and I assume most pharmacists would do it the same way.

Dan Lessler, MD: Okay. Bob?

Robert Bray, MD: Dr. Bray. Let me offer maybe a compromise, and maybe it's unnecessary, but to me the only thing that I would want to be clear about is if I write for an immediate release product that it would be substituted with another immediate release product and if I wrote for a long-acting product it would be substituted with another long-acting product. And I- I think Janet's point is well taken and really these drugs don't have a tremendous amount of titration. You know, usually there's one or two dosing forms and there's not a lot of variability in there that would make me concerned that this might be- that there might be major mistakes in that process. And like you say, you can always just- if it's unclear, that gets a call and that motivates me to be a lot more clear next time because I don't want to take that call.

T. Vyn Reese, MD: Okay. Why don't we just delete what I just said. These can be subject to therapeutic interchange on the Washington Preferred Drug List. But I agree, if you wrote for a long-acting one and you had a reason to do it you shouldn't substitute a short-acting one and that should be taken care of by adding a long-acting drug. Right?

Male: Right. Correct.

Dan Lessler, MD: So we really wouldn't need to state that- I'm asking the question, I guess, of Siri and others. If we wrote for a long-acting form it would be substituted- if there was substitution to be done it would be substituted for another long-acting form, correct?

Siri Childs, Pharm D: I think if that's what you want you should say it.

T. Vyn Reese, MD: So in other words I need to add that to the end. Okay. Immediate release forms cannot be therapeutically interchanged for long-acting forms. And vice versa.

Dan Lessler, MD: So, just to reiterate for Jason who does not have the benefit of Power Point here. Where we're at is, After considering the evidence of safety, efficacy and special populations for the treatment of overactive bladder, I, this is Dr. Reese, move that Darifenacin, Oxybutynin, Solifenacin, Tolterodine and Trospium are safe and efficacious. No single incontinence medication is associated with fewer adverse events in special populations. These drugs can be subject to therapeutic interchange in the Washington Preferred Drug List. Immediate release formulations cannot be interchanged for long-acting formulations and vice versa. One long-acting formulation must be included as preferred drug on the Washington Preferred Drug List.

Male: So moved.

Dan Lessler, MD: Is there a second?

Male: Second.

Dan Lessler, MD: All those in favor?

All: Aye.

Dan Lessler, MD: Opposed [unclear]? Okay. Thanks. We can move on to the last update, which is on the PPIs and I think- Susan, are you on the phone?

Susan Carson, MPH: Yes, I am.

Dan Lessler, MD: Great.

Susan Carson, MPH: Hi.

Dan Lessler, MD: Give us about two minutes to get the slides up.

Susan Carson, MPH: Sure.

Jeff Graham, MD: Susan, this is Jeff again. I wanted to just say we're emphasizing the update slides.

Susan Carson, MPH: Right.

Jeff Graham, MD: Okay. Good.

Dan Lessler, MD: So, we're ready to go. We have the first title slide up; Drug Class Review of Proton Pump Inhibitors and you can take it from there.

Susan Carson, MPH: Okay, great. So this is Update No. 3 of the PPI report. I know you've done this class before so I'll just be highlighting the new information. And I just wanted to let you know we're in the process of conducting update No. 4, which will be released in May, 2006. And the next slide shows our searches. We conducted the [unclear] searches through September 2004. And we also received additional data on four trials of Esomeprazole from the funder, which allowed us to add information to our met analysis of esophagitis healing rates at four and eight weeks. And please skip to slide No. 4. This slide shows the included populations and medications. There were no changes to the key questions or inclusion criteria for this update. Also, for you information, for update No. 4 we'll be adding children and including IV formulations, which are not currently included. And please go to slide No. 7, which is the healing of esophagitis or relief of GERD symptoms. So the major changes to the report this update, or in the section on patients with GERD, we added six new head-to-head trials of patients with GERD for a total of 25 trials, we added a new analysis of esophagitis healing in patients with moderate to severe esophagitis, which was defined as grade [unclear] or grade 3 or 4 depending on the scale used. This was in response to public comment suggesting that we add more information about this subgroup. In this update we also added a new meta analysis of head-to-head esophagitis trials to determine estimates and 95% confidence intervals for symptom relief and healing rates for the individual drugs.

Next slide. Three trials compared Esomeprazole 40 milligrams to Omeprazole 20 milligrams. Two published studies found a higher healing rate for Esomeprazole and one unpublished study found no difference. We were able to pull these studies with new information provided by the funder of the studies, this update. And the pulled risk difference for healing at four weeks was 8% higher for Esomeprazole, and at eight weeks it was 5% higher for Esomeprazole 40 milligrams. And that translates to a number needed to treat at eight weeks of 20.

In other words for every 20 patients treated with Esomeprazole 40 milligrams instead of Omeprazole 20 milligrams, one additional patient would be healed at eight weeks.

Next slide. Three trials compared Esomeprazole 40 milligrams to Lansoprazole 30 milligrams. One of these was new this update and that was Fennerty 2005. In one large, good quality, multi-center study, that's Castol 2002, healing rates were 4% higher for Esomeprazole at four weeks and 3% higher at eight weeks. The other two studies of this comparison found equivalent healing rates at eight weeks. So we pulled these studies and found that Esomeprazole had a 5% higher healing rate at four weeks and a 3% higher healing rate at eight weeks. At eight weeks the confidence interval for this risk difference ranged from 1% to 5%. And the number needed to treat at four weeks was 20, favoring Esomeprazole and at eight weeks the number needed to treat was 33.

Next slide. This slide shows results for complete symptom relief. Pooled estimates of two studies of Esomeprazole 40 milligrams compared with Lansoprazole 30 milligrams- the slide's incorrect, it should say Lansoprazole 30 milligrams. Also two studies of Esomeprazole 40 milligrams versus Pantoprazole 40 milligrams, found no significant difference in complete symptom relief at four weeks. In three studies of Omeprazole 20 milligrams versus Esomeprazole 40 milligrams, Esomeprazole had a 10% higher rate of complete symptom relief at four weeks. Okay.

Next slide. Maintenance of healed esophagitis. There was no new information on maintenance. So just to recap, there's good evidence that there's no difference between Omeprazole and [unclear] and Rabeprazole. The longest study was of Omeprazole versus Rabeprazole and that was five years. And one six-month study found lower relapse rate for Esomeprazole 20 milligrams compared with Lansoprazole 15 milligrams.

Next slide. The next four slides show the results of our new analysis of esophagitis healing rates in patients with moderate to severe esophagitis. That's grade three or four or C or D. Three studies compared Esomeprazole 40 milligrams to Omeprazole 20 milligrams. The pooled risk difference in these studies was 16% higher for Esomeprazole at four weeks then 13% higher at eight weeks. Two studies compared Esomeprazole 20, that's a lower dose, to Omeprazole 20 and there was no difference at either four weeks or eight weeks.

Next slide. Esomeprazole 40 milligrams was compared to Lansoprazole 30 milligrams in two studies in patients with moderate to severe esophagitis. And we found that the pooled estimate was 8% higher for Esomeprazole at four weeks and 9% higher at eight weeks. In a third study the outcome was reported as either complete healing of esophagitis or improvement by at least two grades. So, for example, from three to one or four to two. And in this study there was no significant difference between Esomeprazole and Lansoprazole, although there was a nonsignificant trend favoring Lansoprazole with a 10% risk difference.

Next slide. One study compared Esomeprazole 40 milligrams to Pantoprazole 40 milligrams in patients with moderate esophagitis. At eight weeks Pantoprazole had a higher healing rate than Esomeprazole. In this study there were no patients with severe or grade D esophagitis. They were all grade C. And they did not report healing rates at four weeks, only at eight weeks.

Next slide. Three studies compared Lansoprazole to Omeprazole in patients with moderate to severe esophagitis. There was no difference in the pooled healing rates at four and eight weeks in two studies comparing Lansoprazole 30 milligrams to Omeprazole 20 milligrams. And that pooled risk difference was 1% at four weeks and 3% at eight weeks. It was nonsignificant. The third study compared Lansoprazole 30 milligrams to Omeprazole 40 milligrams, a higher dose, and found a higher healing rate for Lansoprazole at four and eight weeks, but again the difference was not statistically significant.

Next slide. For the other indications including duodenal ulcer, gastric ulcer and NSAID induced ulcer we added new trials, but their results were consistent with the other evidence already in the report and do not change the conclusions of the report. So please skip all the way to slide No. 23 because we don't have any new information to report.

Slide No. 23 about adverse events, again we found no new comparative information about adverse events. No changes to our conclusion. Slide No. 25, also no new evidence about safety or efficacy in subgroups. So then onto slide 27, which just summarizes esophagitis in the general population for update No. 3. For esophagitis there's good evidence of no difference between Lansoprazole, Pantoprazole, Rabeprazole and Omeprazole for healing or symptom relief. Esomeprazole 40 milligrams was superior to Lansoprazole 30 milligrams for healing in one study and was equivalent in another two studies. And there was a pooled risk difference of 4% at four weeks and 3% at eight weeks for that comparison favoring Esomeprazole. And Pantoprazole 40 milligrams was equivalent to Esomeprazole 40 milligrams for symptom relief at four weeks.

Next slide summarizes our evidence for the analysis for moderate to severe esophagitis and we found that Esomeprazole 40 was superior to Omeprazole 20 at both four and eight weeks, but no difference between Esomeprazole 20 compared to Omeprazole 20. Esomeprazole 40 was superior to Lansoprazole 30, but Pantoprazole 40 was superior to Esomeprazole 40. And Lansoprazole 30-Lansoprazole versus Omeprazole had mixed results.

Next slide. Our conclusions for ulcer and eradication of H. Pylori remain the same. And onto slide 31, conclusions for adverse events in subgroups remain the same, as I already said. No evidence of a difference in short-term studies. And insufficient evidence to establish any differences between PPIs in subgroups based on age, gender or ethnicity. And that's the end of the presentation. Thank you.

Dan Lessler, MD: Thank you, Susan. I was going to open it up to questions from the committee for Susan on the presentation and the update. Any questions or points of clarification. Okay. Susan, if you'll just stay on the phone for another couple minutes, we're going to take stakeholder input.

Susan Carson, MPH: Sure.

Dan Lessler, MD: Sometimes we like to come back to you for clarification on…

Susan Carson, MPH: Okay.

Dan Lessler, MD: [unclear]. Actually, we have two people who have signed up for comment. First is Nancy Weeks from Wyeth.

Nancy Weeks: Hi, I'm Nancy Weeks with Wyeth Pharmaceuticals. I'd like to thank you very much for your time today. I am an area account manager based out of Seattle, Washington. And I am here to just bring up some key points about Protonix, oral and IV. As can be seen by your very thorough report, the proton pump inhibitors as a class are therapeutically equivalent. And I'm not here to say that Protonix is any better than any of the other PPIs because as you can clearly see by the pooled data, that's not the case. They're all very good medications and far superior than HRSA's. Some key points I'd like to bring up regarding Protonix is compliance seems to be a major problem amongst the population that we serve within Washington State. I believe that the average script was for 36 days of therapy for oral PPIs for the Medicaid patients and compliance seems to be a major problem. Any way in which you can select a medication that could possibly increase patient compliance can certainly be most helpful to the patient. As was mentioned here earlier, there's nothing worse than having a bottle full of pills that aren't being used. So Protonix is a small, easy to swallow tablet for those elderly patients you mentioned earlier up in the front, that there were roughly a couple hundred thousand elderly patients. In addition to that those patients who maybe have difficulty swallowing. Smaller, easy to swallow tablet can enhance patient compliance. Secondly, the fact that it's a 40 milligram, once daily dosing can be taken with or without food. C-max and area under the curve is not affect by food. With some of your other proton pump inhibitors C-max and area under the curve can be affected significantly depending on the timing and the dosing of the drug. Third point I'd like to make, as was mentioned in table 10 of the EPC report, there was extensive studies done with Protonix with regards to drug/drug interaction and as can be seen by your report there were no other significant drug/drug interactions as compared to the other proton pump inhibitors. Protonix had the least known drug/drug interactions. For those patients who may be poly pharmaceutical, for the elderly patients, drug interactions is a concern and the less things you have to worry about as a physician, as a pharmacist, the better life can be for everybody. Next point I'd like to make is continuum of care. Protonix, oral and IV, is- both products are preferred formulary in most of the Washington State hospitals. I cover downtown Seattle. Protonix oral and IV are the preferred PPI agents. University of Washington, Harborview Medical Center, Swedish Providence, [unclear] up in Bellingham, Multicare, Franciscan Health System down in Tacoma, Auburn Regional, hospitals all up and down the east side of Lake Washington, Stevens Hospital, Sacred Heart out in Spokane, Good Sam out in Puyallup. As you can see here, patients who were started in the hospital on Protonix IV can easily be transitioned to Protonix oral once they get the discharge from the hospital. You don't have to worry about the patient having a sudden adverse event because they're on a new medication. Continuum of care, knowing that the patient's done well in the hospital on this product, that they need to go into the outpatient setting on oral medication, that it's equivalent and that there will be no surprises. And the last point I'd like to make is that you are dealing with a younger, healthier population and that Protonix oral is pregnancy category B. I thank you very much for your time and I do hope that you will give serious consideration for considering Protonix to be added to the PDL. Thank you.

Dan Lessler, MD: Thank you. Next is Dr. Lein.

Diana Lein: Good morning. My name is Diana Orentas Lein and I am a scientific affairs liaison for Santarus and I want to thank you all for the opportunity to present some information about Santarus' product, Zegerid, which is a unique immediate

release formulation of Omeprazole, which is a powder for oral suspension. Because Zegerid was approved in the last year it was not included in the review, however I would like to take this opportunity to present some pertinent information which may be of particular interest to this committee. As you know, all PPIs are acid labile, and for that reason they need to be protected from gastric acidity. This is to avoid inactivation and degradation of the prodrug. Today all the marketed PPIs use an enteric coating to delay the release of the PPI until it's moved past the gastric environment and into the small bowel. In contrast, what Santarus has done is buffered the gastric acidity with sodium bicarbonate, which is administered together with the PPI micronized Omeprazole. The combination of micronized Omeprazole together with the sodium bicarbonate leads to a rapid neutralization of gastric acidity allowing for protection of the prodrug and immediate or rapid absorption of the PPI. Peak plasma levels occur within 30 minutes after administration of the drugs and the Cmax is greater than 50% higher than that seen with the delayed released of Omeprazole product Prilosec. In fact, because of the unique pharmokinetic properties, Zegerid has been classified by the FDA as the only product in a new class of immediate release PPIs, and as such is not AB rated when compared to any other Omeprazole product.

In the Pharmaco dynamic trials once daily 40 milligram Zegerid raised gastric ph greater than four for 18.6 hours per day, demonstrating excellent ph control. In a study published in April in the journal Critical Care Medicine when 40 milligrams of Zegerid was administered to critically ill patients through an NG tube, it demonstrated rapid and sustained gastric ph greater than four. In fact, the median ph was greater than six on all 14 trial days for the Zegerid arm. This led to their approval by the FDA of Zegerid for the reduction of risk of upper GI bleeding in the critically ill patient. Zegerid is now the only PPI with this indication. In addition to being the only PPI indicated for the reduction of risk of upper GI bleeding in the critically ill patient, Zegerid is also approved for the treatment of duodenal ulcer, symptomatic GERD, erosive esophagitis, maintenance of healing erosive esophagitis and treatment of active benign gastric ulcer.

In closing, in last year's PPI review there was some discussion about the need for a liquid formulation for special populations, and we feel that Zegerid meets that need, especially in patients with an NG tube, patients with dysphasia and patients that have difficulty swallowing. Thank you.

Dan Lessler, MD: Thank you.

Diana Lein: Do you have any questions?

Dan Lessler, MD: I don't think so. Thanks.

Diana Lein: Okay. Thank you.

Dan Lessler, MD: Okay. Are there any questions for Sue? You still on the phone at this point, before…okay. Sue, thank you very much.

Susan Carson, MPH: Oh, you're welcome. Hey, I was given a note from- regarding the OAB's report. Marion wanted to just add something to this- her response to the public comment.

Dan Lessler, MD: Maybe we can do that- well, Jeff, what were you going to say?

Jeff Graham, MD: I was just going to say maybe she can mail it to us [unclear].

Susan Carson, MPH: Gotcha. Okay. All right. All right. I'll convey that to her. Well, thank you.

Dan Lessler, MD: Thanks.

Susan Carson, MPH: Okay. Bye.

Dan Lessler, MD: Bye-bye. So, actually, I'm wondering if we might not just look at the last motion from September from 2004, actually that Dr. Reese had made. And I'm wondering if people could take a look at that, if anybody's feeling, based on new evidence, if there's any need to change that at this point.

T. Vyn Reese, MD: This is Dr. Reese. Yeah, I don't see any- it sounds like it's pretty much the same. Unless anyone sees any other changes we need to add to that motion. I think we can just move to have that motion…

Dan Lessler, MD: Hold on before you do it- Bob had a comment.

Robert Bray, MD: I was going to say what he said.

Dan Lessler, MD: You're seconding the motion. So, the record will show then that Dr. Reese made the motion, Dr. Bray seconded, which is to leave the current recommendation that was made September 15th, 2004, meeting in place. Is there any discussion? All those in favor say Aye.

All: Aye.

Dan Lessler, MD: Opposed, same sign. Okay. So, I think at this point we can take a 15 minute break and probably even convene at- maybe we can take an 18 minute break and reconvene at five of three.

Duane Thurman: Dr. Lessler- this is Duane Thurman. Give me one minute. I just want to thank the committee on behalf of the agencies participating in the project and the governor's office. I think that we've attracted a lot of attention; you're going to hear a lot about evidence-based medicine as we go into the session with some of the governor's initiatives. And for good or for bad, I think that people will begin scrutinizing what our process has done as an example of this and I just really appreciate all the hard work and dedication you guys have done, because this has been a very difficult project and we will move forward through the new year. So thank you very much.

Dan Lessler, MD: Thank you.

DUR Board Meeting Minutes
December 21, 2005

WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING

Regular Meeting

Radisson Hotel SeaTac

2:00pm – 4:00pm

Council Members Attending: Daniel Lessler, MD; Alvin Goo, Pharm; Patti Varley, ARNP; Carol Cordy, MD; Robert Bray, MD; T. Vyn Reese, MD; Angelo Ballasiotes, Pharm D.; Jason Iltz, Pharm D.; and Janet Kelly, Pharm D.

Health and Recovery Services Administration (HRSA), Division of Medical Management Coordinating Staff: Jeff Thompson, MD, DMM Chief Medical Officer; Siri Childs, Pharm D, Pharmacy Policy Office Chief; Nicole Nguyen, Pharm D, Clinical Staff Pharmacist.

I. ADMINISTRATIVE ITEMS

The meeting was brought to order by chairperson, Daniel Lessler, MD.

II. Poly-pharmacy for Dual Eligibles

Dr. Jeffrey Thompson, Chief Medical Officer for HRSA, provided a presentation of a Medicaid pharmacy intervention to reduce poly pharmacy in the dual eligibles. Starting January 1, 2005 these clients will be transferred to the Medicare Part D Prescription Program and will have $1.00 to $3.00 copays for each prescription. There are about 95,000 dual eligible clients and these clients account for 48% of the fee for service pharmacy dollars spent. The average number of prescriptions these clients receive a month are 7, with some clients receiving more than 20 prescriptions a month. This intervention targeted 299 clients with ten or more prescriptions a month and two or more prescribers. A prescription history print out was sent to the prescribers of these clients. Prescribers were asked to coordinate with the other prescribers to consolidate drug therapy when appropriate, stop duplicate therapy, and compare the client's drug regimen to the Medicare Part D PDP formulary to determine if the drugs are covered. 46% of prescribers found the information useful but did not make changes, 6% discontinued drugs, and 11% found the information not useful.

III. Therapeutic Duplication of Atypical Antipsychotics

Dr. Jeffrey Thompson presented the status of the Mental Health Drugs Workgroup's work on duplication of the atypical antipsychotics. The number of clients with duplication of each drug combination for 3 out of 3 months is known and being reviewed. There are over 2000 clients receiving drug therapy with multiple atypicals totally over $5 Million in 4th quarter 2004. The dosages of the drugs will also be reviewed.

IV. MANUFACTURERS' PRESENTATION

None

V. STAKEHOLDERS' PRESENTATIONS

None

VI. RECOMMENDATIONS OF COUNCIL

The presentation was informational only.

ADJOURNMENT